

**Figure 2.** Tumor-treating field (TTFields)-sensitizing effects of sorafenib on glioblastoma in vivo. (A) Nude mice were inoculated with U373 cells and treated with TTFields, sorafenib, or a combination thereof. Tumor volumes were measured at the indicated time points using the formula: volume (length  $\times$  width<sup>2</sup>  $\times$  3.14)/6 ( $n = 8$ ) \*  $p < 0.05$ . (B) Images of tumors isolated from control- or TTFields-treated mice,  $n = 4$ . Sora: sorafenib; bar = 1 cm. (C) Tumors were excised and weighed at the end of the experiment (seven days) \*  $p < 0.05$ ; \*\*  $p < 0.01$ ; (D) Representative PET/CT images of U373 tumor-bearing mice after injection of [<sup>18</sup>F] fluorodeoxyglucose (FDG). The radioactivity of [<sup>18</sup>F] FDG in tumors is presented as the maximum standard uptake value (mean  $\pm$  SD). \*  $p < 0.05$ ; SUV: Standard uptake value. (E) Hematoxylin and eosin (H&E) staining and Ki-67 expression was examined by immunohistochemistry. \*  $p < 0.05$ ; \*\*  $p < 0.01$ ;  $n = 4$ ; Solid circle: Control; Solid square: Sorafenib; Sorafenib; Triangle: Tumor-treating field; Inverted triangle: Sorafenib+TTF. (F) The body weights of the mice were not significantly different among the sorafenib, TTFields, and combination-treated groups,  $n = 4$ ; (G) The spleen, liver, and lung tissues of the mice were excised and weighed at the end of the experiment (seven days),  $n = 4$ .

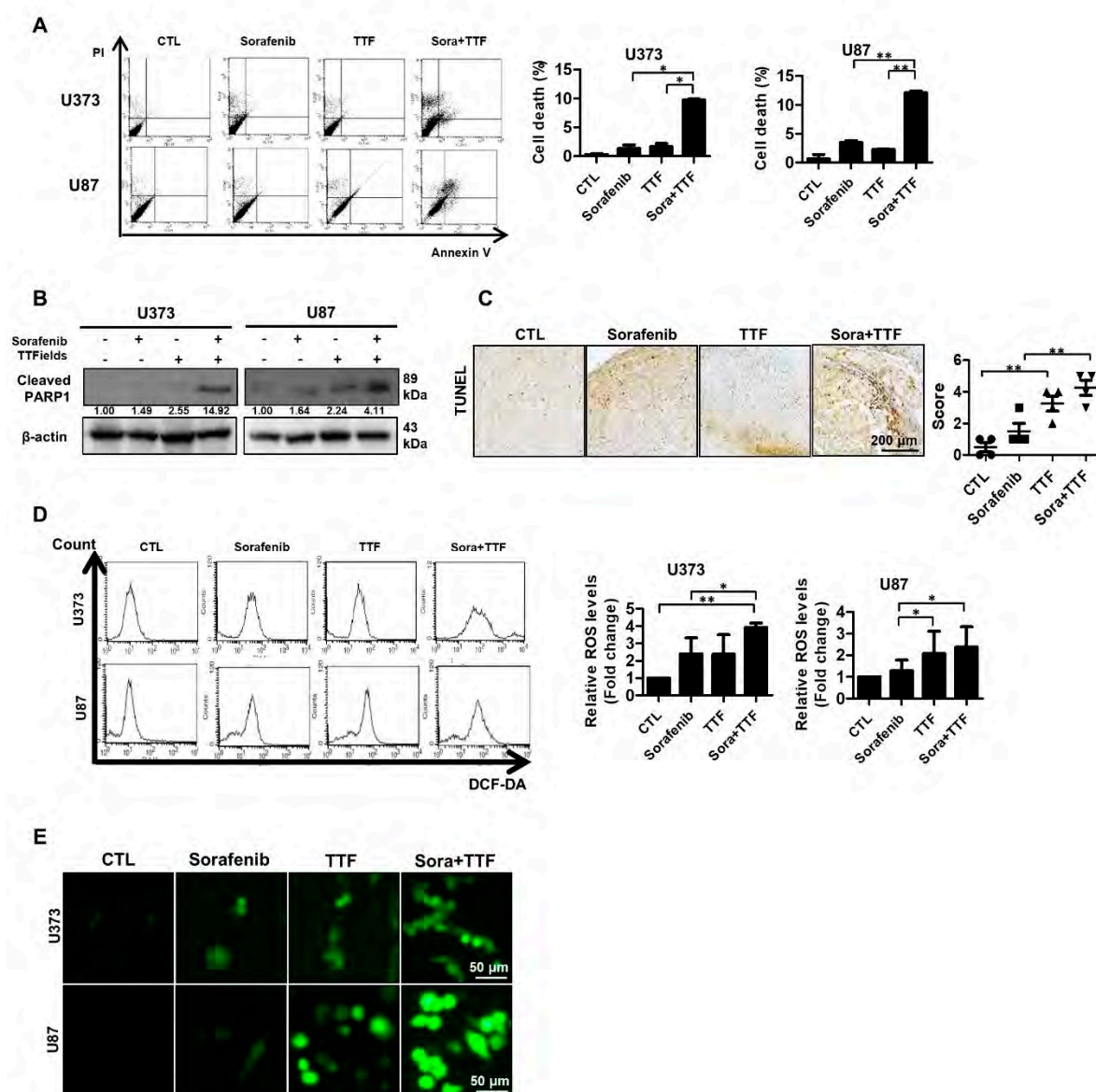
### 2.3. Sorafenib Enhances TTFields-Induced Apoptosis



### Int. J. Mol. Sci. 2018, 19, x FOR PEER REVIEW 2.3. Sorafenib Enhances TTFields-Induced Apoptosis

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To investigate whether sorafenib and TTFields induce apoptosis, we assessed early apoptosis via annexin V and propidium iodide staining. In the two glioblastoma cancer cell lines, 48-h exposure to sorafenib plus TTFields significantly increased the proportion of early apoptotic cells (Figure 3A). Thereafter, we investigated whether sorafenib-enhanced TTFields cytotoxicity resulted from increased PARP cleavage, leading to enhanced apoptotic cell death. We observed increased PARP cleavage in response to combined TTFields and sorafenib treatment when compared to treatment with sorafenib alone (Figure 3B). To determine whether combinatorial therapy induces apoptosis *in vivo*, we evaluated the apoptotic rate using a terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) assay. Apoptotic cell death was increased upon combinatorial treatment (Figure 3C). We also investigated the association between ROS production and enhancement of TTFields-induced apoptosis by sorafenib. ROS production was more strongly induced upon combinatorial treatment than upon individual treatments (Figure 3D), which may explain the increased apoptotic rate upon combinatorial treatment. These data are consistent with the results of fluorescence microscopy, as shown in Figure 3E.



**Figure 3.** Effects of sorafenib and tumor treating fields (TTFields) on apoptosis in glioblastoma cells.

(A) U373 and U87 cells were exposed to sorafenib (5  $\mu\text{mol/L}$ ) and/or TTFields for 48 h prior to annexin V/PI staining; (B) cell lysates (30  $\mu\text{g}$ ) were immunoblotted with antibodies against cleaved PARP1 and  $\beta$ -actin. Band intensities were quantified and normalized to actin intensities ( $n = 3$ , mean

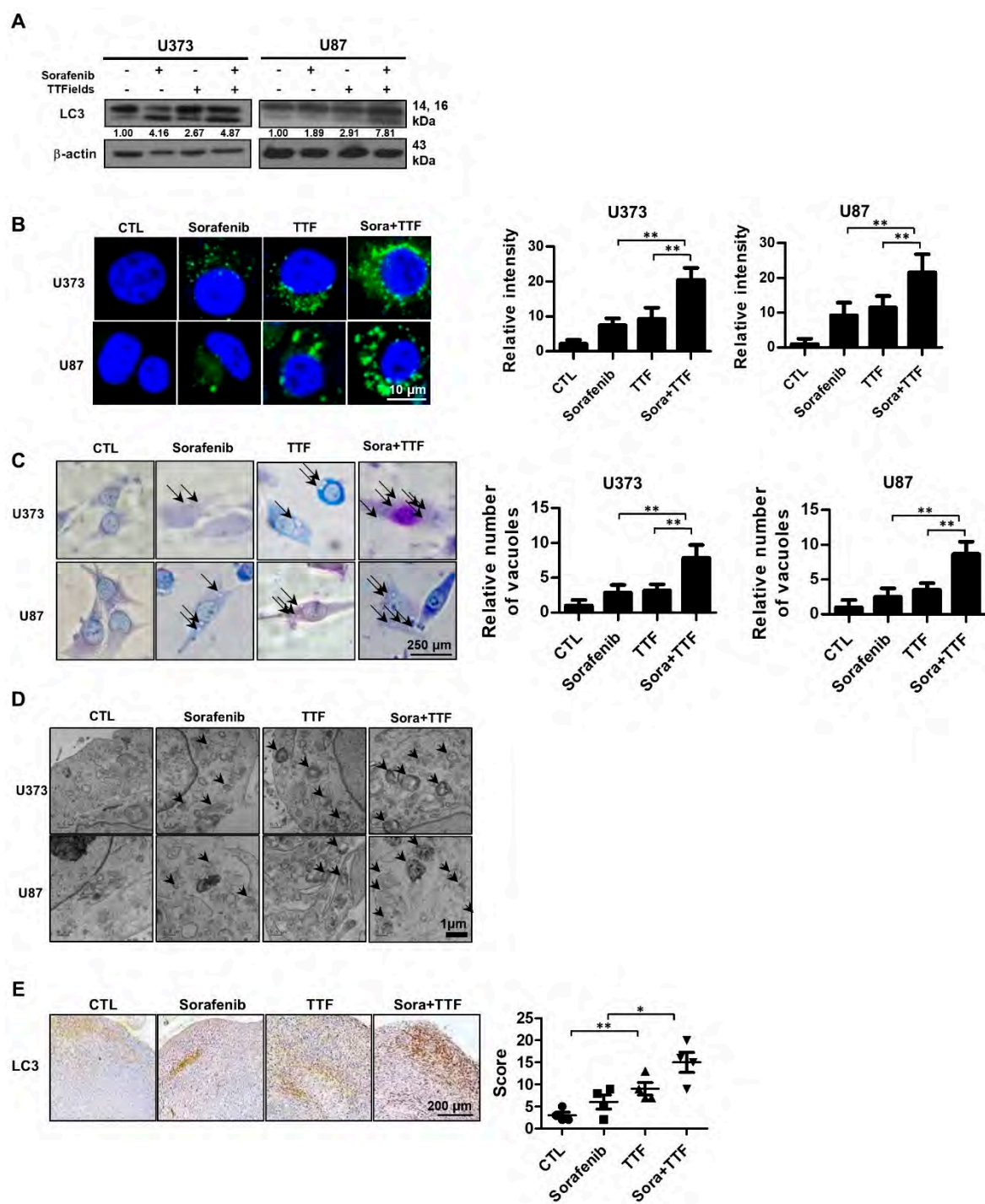


(A) U373 and U87 cells were exposed to sorafenib (5  $\mu\text{mol/L}$ ) and/or TTFields for 48 h prior to annexin V/PI staining; (B) cell lysates (30  $\mu\text{g}$ ) were immunoblotted with antibodies against cleaved PARP1 and  $\beta$ -actin; Band intensities were quantified and normalized to actin intensities ( $n = 3$ , mean  $\pm$  SD). (C) terminal deoxynucleotide transferase-mediated dUTP nick-end labeling assays were performed using xenografts,  $n = 4$ ; Solid circle: Control; Solid square: Sorafenib; Triangle: Tumor treating fields; Inverted triangle: Sorafenib+TTF. (D,E) U373 and U87 cells were treated with sorafenib, TTFields, or the indicated combinations, and reactive oxygen species (ROS) levels were determined using 2',7'-dichlorofluorescein diacetate (a peroxide-sensitive dye), flow cytometry, and confocal laser fluorescence microscopy. Data are expressed as % of control and are means  $\pm$  SD from 3 experiments. \*  $p < 0.05$ ; \*\*  $p < 0.01$ .

#### 2.4. Effects of Sorafenib and TTFields on Autophagic Cell Death

To investigate the anticancer effects of sorafenib and TTFields further, we examined other cellular responses associated with cell death upon sorafenib or TTFields treatment; in particular, we investigated the effects on autophagy, since both TTFields and sorafenib induce autophagy [20,30]. Western blotting revealed that the levels of LC3, a specific marker of autophagosome generation, were increased in cells administered combinatorial treatment (Figure 4A). As shown in Figure 4B, increased accumulation of Cyto-ID Green, an autophagy indicator, was observed around combination-treated U373 and U87 cells. After 48 h of treatment with TTFields plus sorafenib, Giemsa-stained U373 and U87 cells exhibited ultrastructural changes in the whole cytoplasm and membranes, including loss of plasma membrane integrity and distinct vacuole formation, compared to those receiving individual treatments (Figure 4C). This drastic vacuolization of the cytoplasm without apparent loss of nuclear material is consistent with the described macrostructure of autophagosomes. In addition, transmission electron microscopy was used to verify autophagosome formation in cells receiving combinatorial treatment. As shown in Figure 4D, cells administered combinatorial treatment exhibited accumulation of large autophagic vacuoles with a typical double-layer membrane and organelle remnants, whereas only a few vacuoles were observed in cells receiving individual treatments. In addition, mouse xenografts were stained for LC3 to clarify whether sorafenib combined with TTFields could additionally induce autophagy in vivo compared to the individual treatments (Figure 4E). Collectively, our data showed that autophagy contributes to glioblastoma cell death after combinatorial treatment in vitro and in vivo.





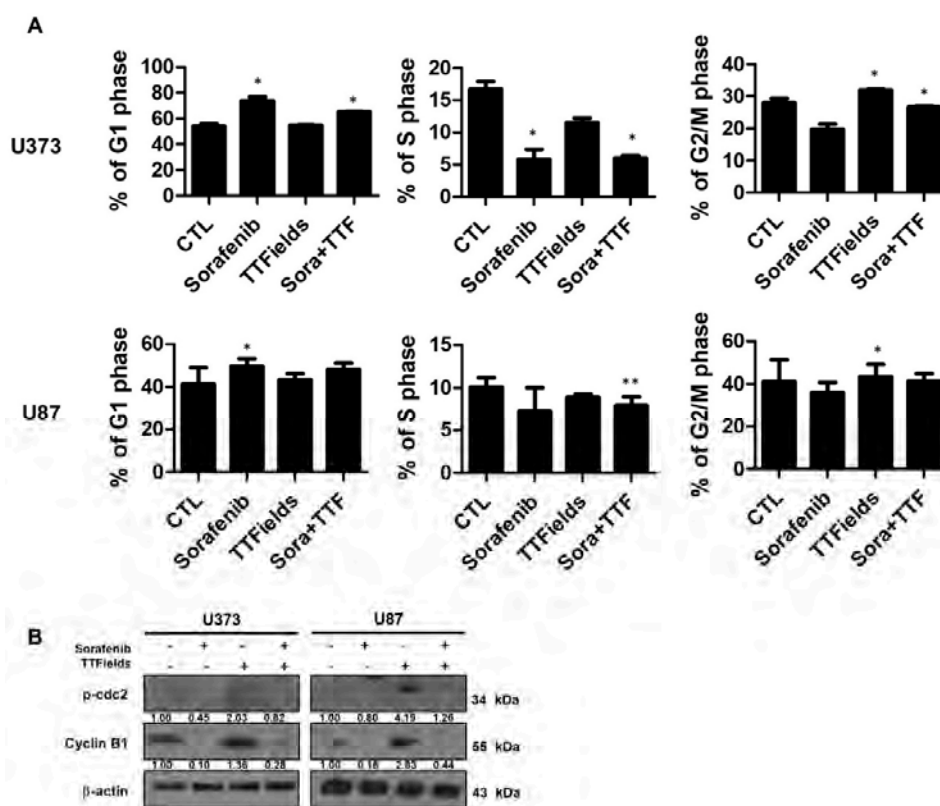
**Figure 4.** Combinatorial treatment with sorafenib and tumor treating fields (TTFs) induces autophagy in glioblastoma cancer cells. (A) cell lysates (30  $\mu$ g) were immunoblotted with anti-LC3 and anti- $\beta$ -actin antibodies. Band intensities were quantified and normalized to actin intensities ( $\beta$  = mean  $\pm$  SD). (B) Cytofluorescence of U373 and U87 cells with and without sorafenib, sorafenib and with and TTFs treatment. \*  $p < 0.01$ . (C) cells were stained with Giemsa stain (10% in phosphate buffered saline), washed and imaged using a Leica DM IRB light microscope (magnification  $\times 40$ ). Black arrows indicate vacuoles ( $\times 40$ ). (D) Autophagy vacuoles were assessed by transmission electron microscopy in cells. Black arrow: autophagic vacuoles. (E) LC3 expression in xenografts was examined by immunohistochemistry. Representative images are presented. \*  $p < 0.05$ ; \*\*  $p < 0.01$ . Solid circle: Control; Solid square: Sorafenib; Triangle: Tumor treating fields; Inverted triangle: Sorafenib+TTF.

## 2.5. Effects of Sorafenib and TTFs on the Cell Cycle



## 2.5. Effects of Sorafenib and TTFields on the Cell Cycle

We analyzed cells treated with 5  $\mu$ M sorafenib or TTFields for 24 h by using propidium iodide staining and flow cytometry to evaluate the effect of sorafenib treatment on cell cycle progression in human glioblastoma cells. Sorafenib treatment increased the proportion of cells in the G1 phase and markedly decreased the proportion of cells in the S phase in comparison with the control treatment (Figure 5A). Similar results were obtained when using U87 cells. When the U373 and U87 cells were exposed to TTFields alone for 24 h, a small fraction of the cells in the G1 and G2/M phases and the percentage of cells in the G1 and S phases also decreased. Upon pretreatment with sorafenib, the TTFields-induced G2/M phase arrest decreased within 24 h after treatment with sorafenib, with an increase in the percentage of cells in the G1 phase compared with that observed with TTFields alone. Western blotting indicated that TTFields alone led to significant accumulation of cyclin B and p-CDC2, which are key regulators of the G2/M transition (Figure 5B). Combinatorial treatment with sorafenib suppressed the TTFields-induced accumulation of these markers.



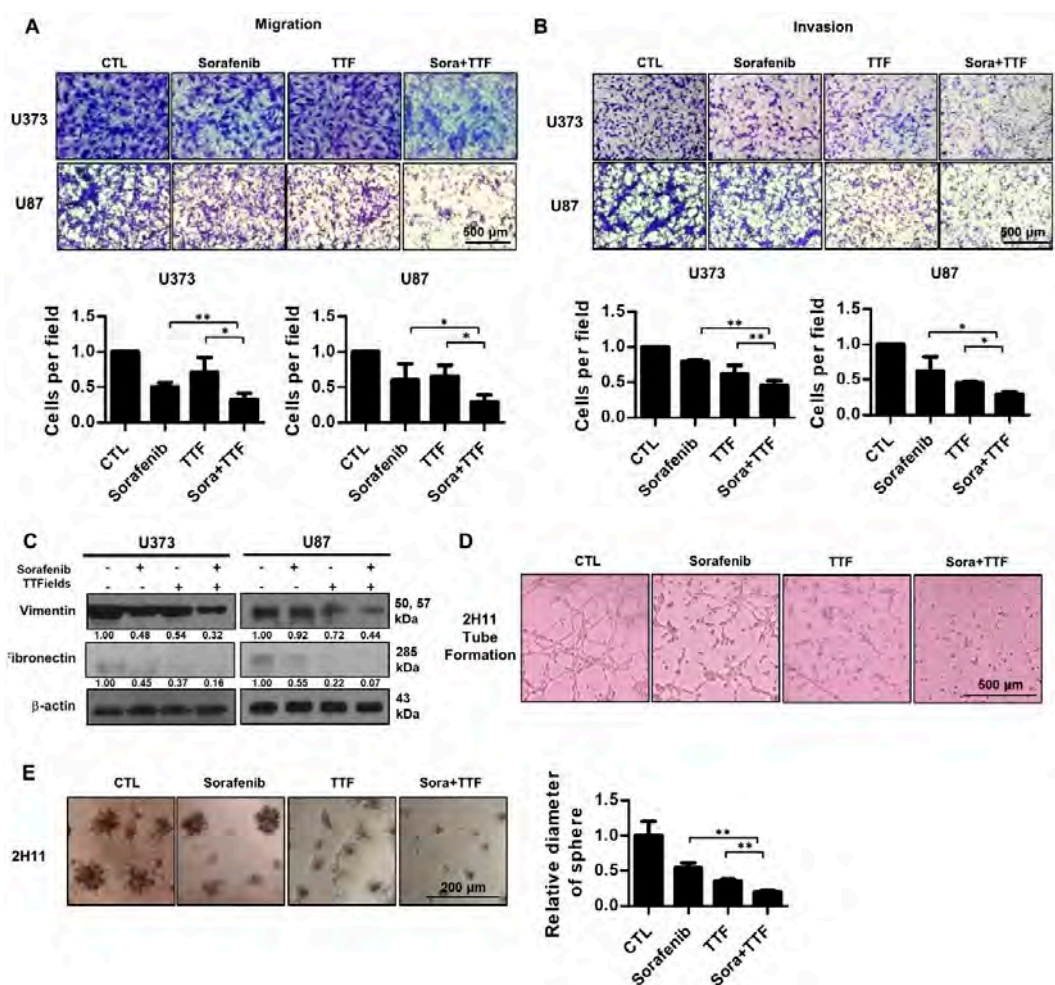
**Figure 5.** Sorafenib plus tumor-treating fields (TTFields) inhibits cell cycle progression in glioblastoma cells. (A) U373 and U87 cells were treated with sorafenib (5  $\mu$ M) and/or 0.9 V/cm TTFields for 24 h. Cell cycle distribution was analyzed quantitatively by flow cytometry (bars: 0.05; 0.05; 0.01; 0.01). (B) phospho-cdc2 and cyclin B1 expression analyzed by Western blotting. Blots were stained as a loading control. Equal amounts of protein (5  $\mu$ g) were electrophoresed and analyzed. Band intensities were quantified and normalized to actin intensities (3 mean  $\pm$  SD).

## 2.6. Combinatorial Treatment Significantly Inhibits Tumor Cell Motility and Invasion and Angiogenesis

To determine whether sorafenib regulates the effects of TTFields on metastasis, we examined the effects of sorafenib and TTFields on U373 and U87 cell migration. A Transwell chamber assay revealed that combinatorial treatment decreased cell migration in the U373 and U87 cell lines after 24 h (Figure 6A). Furthermore, using a Matrigel invasion assay, we investigated whether sorafenib and TTFields could affect the invasiveness of glioblastoma cells. Serum-starved cells were seeded in the upper chambers of the Transwell assay system, and the cells that penetrated the Matrigel barrier



in the upper chambers of the Transwell assay system, and the cells that penetrated the Matrigel barrier in response to a chemoattractant (serum) were counted at various time points. Combinatorial treatment significantly decreased the number of invading U373 and U87 cells as compared to the individual treatments (Figure 6B). Together, these results suggested that sorafenib plus TTFields might effectively inhibit the migration and invasiveness of human glioblastoma cells. To investigate the molecular mechanism underlying the modulation of the expression of epithelial-to-mesenchymal transition markers by combinatorial treatment, Western blotting was used. Vimentin and fibronectin, mesenchymal markers, were downregulated in both cell lines (Figure 6C). Furthermore, we examined whether the combinatorial treatment would block angiogenesis. Combinatorial treatment completely inhibited tube formation in 2H11 cells compared with the individual treatments (Figure 6D); in addition, colonies formed in control 3D 2H11 cell cultures were larger than colonies formed by cells treated with TTFields or sorafenib alone, whereas colonies formed by cells treated with the combination were the smallest (Figure 6E).



**Figure 6.** Effect of combinatorial treatment with Sorafenib and tumor treating fields (TTFields) on the invasiveness and migration of glioblastoma cells. (A) tumor cell migration was assessed using a Transwell chamber assay;  $p < 0.05$ ;  $**p < 0.01$  bar = 500  $\mu$ m; (B) tumor cell invasion was assessed using a Matrigel invasion assay;  $*p < 0.05$ ;  $**p < 0.01$  bar = 500  $\mu$ m; (C) cell lysates prepared from sorafenib-, TTFields-, and sorafenib plus TTFields-treated cells were used in Western blotting using antibodies against vimentin and fibronectin; Band intensities were quantified and normalized to actin intensities ( $n = 3$ , mean  $\pm$  SD); (D) tube formation assay using 2H11 cells subjected to the indicated treatments; (E) 3D colony cultures of 2H11 cells treated as indicated.  $**p < 0.01$ .



### 3. Discussion

This study aimed to investigate the mechanism underlying TTFields sensitization of glioblastoma cells by sorafenib to facilitate the clinical use of sorafenib as a TTFields sensitizer. The Food and Drug Administration (FDA) approved the use of TTFields for recurrent glioblastoma [31]. Recently, a phase III clinical study reported that the use of a combination of 200-kHz TTFields and adjuvant TMZ to treat newly diagnosed glioblastoma enhanced both progression-free and overall survival [31]. Based on this finding, the FDA recently approved the use of TTFields to treat newly diagnosed glioblastoma. While this treatment system is very advanced, to obtain improved clinical outcomes, clinically effective drugs need to be used with TTFields. Among anticancer drugs, we focused on sorafenib, a well-known multikinase inhibitor. The availability of drugs targeting novel cellular pathways has increased the possibility of developing improved treatments for glioblastoma patients. Studies on various angiogenesis inhibitors have highlighted the importance of angiogenesis in cancer growth and progression. Recently, several clinical trials have been initiated to evaluate the use of sorafenib in combination with various anticancer drugs to treat various tumors. The most promising evidence of antitumor activity was observed when sorafenib was combined with interferon- $\alpha$  in renal cell carcinoma, dacarbazine in melanoma, doxorubicin in hepatocellular carcinoma, and gemcitabine in ovarian cancer [24]. Moreover, the combination of sorafenib and another targeted agent, bevacizumab, yielded remarkable antitumor effects in ovarian cancer patients [25], and other clinical studies have reported that the combination of sorafenib and radiation might provide clinical benefits in treating various cancers, including glioblastoma [22,26,27]. However, the mechanism underlying TTFields-mediated enhancement appears somewhat more complex than predicted previously in studies on glioblastoma.

We aimed to provide a scientific rationale for the clinical application of sorafenib as a TTFields sensitizer in glioblastoma treatment. Our results suggest that sorafenib significantly enhances the therapeutic efficiency of TTFields through inhibition of tumor cell survival, apoptosis, cell cycle regulation, autophagy, inhibition of tumor cell invasiveness, and inhibition of angiogenesis in human glioblastoma cell lines. Combinatorial treatment with sorafenib and TTFields inhibited the proliferation of U373 and U87 cells in vitro (Figure 1). Moreover, in nude mice bearing xenografts of U373 glioblastoma cells, combinatorial treatment inhibited tumor growth and prolonged the survival of the animals (Figure 2). Notably, sorafenib at concentrations  $>5 \mu\text{M}$  induced significant cytotoxicity. Sorafenib-treated cells were more sensitive to TTFields than non-treated cells (Figure 1b). These results showed that sorafenib enhanced the sensitivity of U373 and U87 cells to TTFields. Combination with sorafenib significantly enhanced the sensitivity of glioblastoma cancer cells to TTFields by promoting apoptosis via increased ROS production (Figure 3). In addition, sorafenib increased autophagy induced by TTFields (Figure 4). Flow cytometry revealed that treatment with sorafenib, alone or in combination with TTFields, inhibited cell cycle progression (Figure 5). Administration of TTFields with sorafenib significantly decreased invasiveness and angiogenesis (Figure 6).

Despite this combinatorial effect, the critical persistent issue is that the treatment of glioblastoma is complicated by the blood–brain barrier (BBB), which is a physiological obstacle for drug delivery to the central nervous system. The effect of TTFields on the BBB is yet unclear. Various tools have been developed for local drug delivery to brain tumors, including convection-enhanced delivery [32]. Local delivery of sorafenib to malignant cells in the brain may increase the effectiveness of antitumor activity with reduced systemic toxicity. Sorafenib exhibited high tolerability and promising antitumor effects in clinical trials in various types of solid tumors [33–35]. Thus, sorafenib is a potentially promising drug to treat malignant gliomas in combination with TTFields. There is a need for optimizing clinical trials of electric field-based tumor treatments via preclinical testing using patient samples and the application of electric fields alone or in combination with drugs. Furthermore, an ideal TTFields sensitizer enhances the sensitivity of tumor cells to TTFields and is harmless to or protects normal tissue. It is unclear whether sorafenib protects normal tissues in combined treatment with TTFields. However, despite the numerous clinical trials of sorafenib for various solid tumors, interest in clinical



trials on glioblastoma remains low. Patients with glioblastoma, however, have few therapeutic options, with most of these options being palliative. The data produced in this study suggest that the use of sorafenib and TTFields is a valid therapeutic option for treating glioblastoma that warrants further investigation. The efficacy of TTFields has been reported in various cancers, such as non-small cell lung cancer, pancreatic cancer, ovarian cancer, mesothelioma, liver cancer, and glioblastoma [10,36]. Sorafenib is also applicable for treating various cancers, such as renal cell carcinoma, hepatocellular carcinoma, and thyroid cancer [24,25,37]. Therefore, combinatorial treatment with sorafenib and TTFields may be effective for treating various cancers in clinical practice.

In line with our findings, Kessler et al. recently reported that combinatorial use of the spindle assembly checkpoint inhibitor MPS1-IN-3 and TTFields to target glioblastoma cells increased apoptosis as well as the rate of cell cycle arrest [38]. However, sorafenib is an anticancer agent that causes cell cycle arrest in the G1 phase. Therefore, unlike MPS1-IN-3, which increased G2/M phase when administered in combination with TTFields, sorafenib reduced it. In addition, both MPS1-IN-3 and sorafenib promoted apoptosis and suppressed proliferation, suggesting that TTFields may produce synergistic effects with various therapeutic agents.

In summary, we report that sorafenib can increase the sensitivity of glioblastoma cancer cells to TTFields through inhibition of tumor cell survival, apoptosis, cell cycle regulation, autophagy, inhibition of tumor cell invasiveness, and inhibition of angiogenesis. These findings provide a molecular basis for the use of chemotherapeutic drugs as TTFields sensitizers to treat cancer. In the future, the identification of TTFields seems to be key for the optimization of therapeutic strategies for glioblastoma.

#### 4. Materials and Methods

##### 4.1. Experimental Setup for Electric Fields

TTFields were generated with a pair of insulated wires (Seoul Electric Wire Co., Ltd., Chungcheongbuk-do, Republic of Korea; outer diameter, 0.4 mm; polyvinyl chloride insulation thickness, 0.17 mm; dielectric breakdown, 25 kV/mm) connected to a function generator (AFG-2112, Good Will Instrument Co., Ltd., Taiwan) and a high-voltage amplifier (A303, A. A. Lab Systems Ltd., Ramat Gan, Israel) that generated sine-wave signals of 0–800 V [39]. To apply the electric field to cells, the insulated wires were attached to the bottom of each cell dish, 1 cm from each other. The applied electric field intensity and frequency was 0.9–1.5 V/cm and 150 kHz, respectively, for all experiments. To confirm the voltage, the same culture dishes as those used in the in vitro experiments were separately prepared, and the voltages applied to the cells were measured using an oscilloscope (GDS-2102A, Good Will Instrument Co. Ltd., New Taipei, Taiwan), while considering the interference caused by the culture dishes [39]. We maintained the frequency at 150 kHz in this experiment because this reportedly is the optimum frequency for U373 glioblastoma cells (cell line used in in vitro experiments) [39].

##### 4.2. Antibodies and Chemicals

Anti-cleaved PARP (#9541), anti-LC3 (#12741) anti-p-cdc2 (#4139), anti-cyclin B (#4138), anti-vimentin (#3932), and anti- $\beta$ -actin (#3700) were purchased from Cell Signaling Technology (Danvers, MA, USA). Anti-fibronectin (ab2413) was purchased from Abcam (Cambridge, UK). Sorafenib tosylate (marketed as Nexavar by Bayer, Leverkusen, Germany) was purchased from Selleckchem (Houston, TX, US). For in vitro experiments, sorafenib was dissolved in dimethyl sulfoxide to generate a 20 mmol/L stock solution, which was stored at 4 °C until use.

##### 4.3. Cell Culture

Human glioblastoma U87 and U373 cell lines were obtained from the Korean Cell Line Bank (Seoul, Korea). U87 and U373 cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), glutamine, hydroxyethyl-piperazineethanesulfonic



acid buffer (HEPES), and antibiotics in a humidified incubator at 37 °C under 5% CO<sub>2</sub>. The murine endothelial cell line 2H11 was cultured in DMEM supplemented with 10% FBS in a humidified 10% CO<sub>2</sub> environment.

#### 4.4. Cell Viability Assay

Cells were seeded at a density of 5000 cells/well in a 96-well plate and incubated for 24 h, in accordance with the indicated experimental conditions. To quantify cell viability, an equal volume of culture medium containing EZ-Cytox reagent (EZ3000, Daeillab Service, Chungcheongbuk-do, Republic of Korea) was added to the cells, and the mixture was incubated for 4 h. Cell viability was determined by measuring the absorbance at 450 nm using a Multiskan EX (Thermo Fisher Scientific; Waltham, MA, US).

#### 4.5. 3D Culture System

Human glioblastoma U373, U87, and 2H11 cells were seeded in 96-well plates at a density of  $1 \times 10^4$  cells/well. The 96-well plates had been precoated with Matrigel as a basement membrane by adding 40 µl of Matrigel to each well, followed by incubation at 37 °C for 30 min. Cells were seeded onto the gel in appropriate medium, and the wells were photographed 10 days later.

#### 4.6. Colony Formation Assay

Cells were subjected to TTFields 6 h after sorafenib exposure at a final concentration of 5 µmol/L, after which cells were incubated for 48 h. After 14–20 days, colonies were stained with 0.4% Crystal Violet (Sigma, St. Louis, MO, USA). The plating efficiency indicates the percentage of seeded cells of a particular cell line that formed colonies under specific culture conditions. The survival fraction, expressed as a function of irradiation, was calculated as follows: survival fraction = colonies counted/(cells seeded  $\times$  plating efficiency/100).

#### 4.7. Tumor Xenografts in Nude Mice

A single-cell suspension ( $2 \times 10^6$  cells) was subcutaneously injected into the flanks of 5-week-old BALB/c nude mice (Nara Biotech; Gyeonggi-do, Republic of Korea). When the tumor reached a minimal volume of 100–200 mm<sup>3</sup>, 1 V/cm TTFields, 30 mg/kg sorafenib (three times a week) via intraperitoneal injections, or the combination were initiated and continued for 7 days. Tumor volumes were determined with the formula  $(L \times l^2)/2$  by measuring tumor length (L) and width (l) with a caliper. The sample size was determined to be 5 per group because this number of mice was required to achieve an effect size of 0.85, a significance level of  $\leq 5\%$ , and a power of  $\geq 80\%$  in Student's *t*-test. Mice that desorbed from the electrodes during TTFields treatment were excluded. There was no randomization when animals were allocated to experimental groups. The trial was approved by Korea University Institutional Review Board (KUIACUC-2018-73, 1 June 2018).

#### 4.8. Positron Emission Tomography (PET)/Computed Tomography (CT) Acquisition

A Siemens Inveon PET scanner (Siemens Medical Solutions, Erlangen, Germany) was used for PET imaging [40]. Before <sup>18</sup>F-fluoro-2-deoxy-d-glucose ([<sup>18</sup>F]-FDG) uptake, the mice were warmed using a heating pad. Thereafter, 200 µCi of [<sup>18</sup>F]-FDG was injected into the tail vein, and the mice were anesthetized with 2% isoflurane in 100% oxygen (Forane solution, ChoongWae Pharma, Seoul, Korea). To acquire anatomical images, X-ray CT data for the mice were acquired with full rotation and 180 projection, using the Inveon system. The exposure time was 200 ms, and the estimated scan time was 504 s for X-ray CT. X-ray CT data were reconstructed using Feldkamp reconstruction (L.A. Feldkamp et al., Dearborn, MI, US) with Shepp and Logan filters. The effective pixel size of the reconstructed X-ray CT image was 109.69 µm  $\times$  109.69 µm. Thirty minutes after tracer uptake and acquisition of X-ray CT data, PET data were acquired for 15 min within an energy window of



350–650 keV. The emission list-mode PET data were sorted into 3D sinograms and reconstructed using OSEM2D methods. The pixel size of the reconstructed images was  $0.38 \times 0.38 \times 0.79 \text{ mm}^3$ . All relevant corrections, such as normalization, dead-time correction, and random correction, were performed for all datasets. X-ray CT data were used to delineate the region of interest (ROI). PET and CT images were coregistered using Inveon Research Workplace (version 2.0, Erlangen, Germany) (Siemens Medical Solutions). After coregistration of the CT and PET data, the ROI was delineated on the CT image and included in the PET data. The maximum pixel values within the ROI on the PET image were then measured and converted to radioactivity cpm values, using a predetermined conversion factor. The standard uptake value was determined by measuring the tissue concentration (MBq/mL)/injected dose (MBq)/body weight (g).

#### 4.9. Detection of Apoptotic Cells via Annexin V Staining

After sorafenib exposure, cells were subjected to TTFields and then incubated for an additional 48 h. The cells were washed with ice-cold phosphate-buffered saline (PBS), trypsinized, and resuspended in  $1 \times$  binding buffer (10 mM HEPES/NaOH [pH 7.4], 140 mM NaCl, and 2.5 mM  $\text{CaCl}_2$ ) to obtain a cell density of  $1 \times 10^6$  cells/mL. Aliquots (100  $\mu\text{L}$ ) of the cell solution were mixed with 5  $\mu\text{L}$  of annexin V conjugated with fluorescein isothiocyanate (PharMingen; San Jose, CA, US) and 10  $\mu\text{L}$  of a propidium iodide stock solution (50  $\mu\text{g/mL}$  in PBS) by gentle vortexing, followed by 15 min of incubation at room temperature in the dark. Buffer (400  $\mu\text{L}$ ,  $1 \times$ ) was added to each sample, and the samples were analyzed on a FACScan flow cytometer (Becton Dickinson, Franklin Lakes, NJ, USA). A minimum of 10,000 cells were counted for each sample, and data were analyzed using CellQuest software (version 6.0, BD Biosciences, San Jose, CA, US).

#### 4.10. Western Blotting

After sorafenib treatment, glioblastoma cells were subjected to TTFields and then incubated for 24 or 48 h. Then, the cells were lysed with Radioimmunoprecipitation (RIPA) buffer; proteins were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and electro-transferred to nitrocellulose membranes. The membranes were blocked with 1% (*v/v*) nonfat dried milk in Tris-buffered saline with 0.05% Tween-20 and incubated with the appropriate antibodies. Primary antibodies were used at a 1:1000 dilution; secondary antibodies, 1:5000. Immunoreactive protein bands were visualized via enhanced chemiluminescence (Amersham Biosciences; Little Chalfont, UK) and scanned.

#### 4.11. TUNEL Assay

Tumors were harvested and fixed with 10% neutral-buffered formalin. Deparaffinized sections were incubated with 20  $\mu\text{g/mL}$  protease K for 15 min at room temperature, washed with PBS, and incubated with the TUNEL reaction mixture (Millipore, Burlington, MA, USA) for 1 h at  $37^\circ\text{C}$  in a humidified chamber. The analysis was carried out in a blinded manner.

#### 4.12. Fluorescence-Based Quantification of Intracellular ROS

The fluorescent probe 2',7'-dichlorofluorescein diacetate (DCFH-DA) was used to quantify intracellular ROS. For fluorocytometric analysis, U373 and U87 cells were treated for 48 h with TTFields, sorafenib, or a combination and were loaded with 10  $\mu\text{M}$  DCFH-DA in 5 mL of PBS min at room temperature for 30. Fluorescence was measured using a flow cytometer (Becton Dickinson, Franklin Lakes, NJ, USA). A minimum of 10,000 cells were counted for each sample, and data were analyzed using CellQuest software (BD Biosciences, San Jose, CA, US). In addition, the DCFH-DA-loaded cells were observed under a confocal laser scanning microscope (LSM 880, ZEISS, Oberkochen, Germany).



#### 4.13. Autophagy Assay

Cells were treated, harvested, stained with Cyto-ID® Green detection reagent (Cyto-ID® Autophagy Detection Kit 2.0, Enzo Life Science, Farmingdale, NY, US) and Hoechst 33342 in accordance with the manufacturer's protocols [41], and observed under a confocal laser scanning microscope (LSM 880).

#### 4.14. Giemsa Staining

U373 and U87 cells were treated for 48 h with TTFields, sorafenib, or a combination of both, and Giemsa staining was performed using a kit from Sigma (St. Louis, MO, US) (GS500). Briefly, cells ( $10^4$  cells/well) were seeded in six-well plates and were allowed to adhere overnight on cover slips, followed by treatment with TTFields, sorafenib, or a combination of both. The cells were fixed with 4% paraformaldehyde for 10 min and stained with Giemsa (10% in PBS) for 15 min, followed by washing with tap water. Images were acquired using a Nikon Eclipse Ts2R-FL (Tokyo, Japan).

#### 4.15. Transmission Electron Microscopy

U373 and U87 cells were treated for 48 h with TTFields, sorafenib, or a combination of both and then fixed in 2.5% glutaraldehyde (Sigma; St. Louis, MO, US). A Sorvall MT5000 microtome (DuPont Instruments, MT5000, Columbus, OH, US) was used to prepare ultrathin sections after dehydration. The sections were stained with lead citrate and/or 1% uranyl acetate, and autophagic vacuoles in the cytoplasmic area were quantified using Image Pro Plus software (version 3, Rockville, MD, US).

#### 4.16. Immunohistochemistry

For immunohistochemical analysis, 4- $\mu$ m-thick paraffin-embedded glioblastoma sections were mounted on coated glass slides to detect proteins of interest. Following antigen retrieval and blocking of endogenous peroxidases and nonspecific protein binding, slide sections were first incubated with primary antibodies (anti-Ki67 and anti-LC3 [1:200]; Cell Signaling Technology, Danvers, MA, USA), followed by incubation with horseradish peroxidase-conjugated secondary antibodies. Slides were developed with 3,3'-diaminobenzidine, followed by hematoxylin counterstaining. The analysis was carried out in a blinded manner.

#### 4.17. Flow Cytometry

Cells were cultured, harvested at the indicated times, and stained with propidium iodide (1  $\mu$ g/mL, Sigma, St. Louis, MO, US) in accordance with the manufacturer's protocol. Then, the cells were analyzed on a FACScan flow cytometer (Becton Dickinson, Franklin Lakes, NJ, USA). A minimum of 10,000 cells were counted for each sample, and data were analyzed using CellQuest software (version 6.0, BD Biosciences; San Jose, CA, US).

#### 4.18. Invasion/Migration Assay

Invasiveness was measured in vitro using Transwell chambers, in accordance with the manufacturer's protocol. Briefly, cells were seeded onto the membrane of the upper chamber of the Transwell at a concentration of  $4 \times 10^5$  cells/mL in 150  $\mu$ L of DMEM and were left untreated or were treated with the indicated doses of sorafenib, TTFields, or a combination of both for 48 h. The medium in the upper chamber was serum-free, whereas that in the lower chamber contained 10% FBS as a source of chemoattractants. Cells that penetrated the Matrigel or gelatin-coated membrane were stained with cell stain solution containing crystal violet, supplied with the Transwell chamber assay (Chemicon, Millipore, Billerica, MA, USA), and were photographed after 48 h of incubation.



#### 4.19. Matrigel-Based In Vitro Endothelial Tube Formation Assay

Endothelial cell tube formation was assessed using Matrigel-coated chamber slides, as described previously [42]. The results of each assay were photographed (Nikon Eclipse Ti microscope with a DS-Fi1 camera, Tokyo, Japan) at a magnification of 40 $\times$ , and the total area occupied by endothelial cell-derived tubes in each chamber was calculated using NIS-Elements-Basic Research software (version number) (Nikon; Tokyo, Japan) and was expressed as an angiogenic score.

#### 4.20. Statistical Analysis

Means were compared using Student's *t*-test. Differences were considered significant if the *p*-value was less than 0.05 or 0.01.

**Author Contributions:** Conceptualization, Y.J. and E.H.K.; Methodology, J.-M.C.; Software, J.S.K. and H.K.; Validation, J.-H.B. and J.-Y.K.; Formal Analysis, Y.J.; Investigation, Y.J.; Resources, S.-G.H.; Data Curation, S.S.; Writing-Original Draft Preparation, E.H.K.; Writing-Review & Editing, Y.J.; Supervision, M.Y.; Project Administration, E.H.K.; Funding Acquisition, E.H.K., S.-G.H. and M.Y.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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ARTICLE

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# Effects of tumor treating fields (TTFields) on glioblastoma cells are augmented by mitotic checkpoint inhibition

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## Abstract

Tumor treating fields (TTFields) are approved for glioblastoma (GBM) therapy. TTFields disrupt cell division by inhibiting spindle fiber formation. Spindle assembly checkpoint (SAC) inhibition combined with antimitotic drugs synergistically decreases glioma cell growth in cell culture and mice. We hypothesized that SAC inhibition will increase TTFields efficacy. Human GBM cells (U-87 MG, GaMG) were treated with TTFields (200 kHz, 1.7 V/cm) and/or the SAC inhibitor MPS1-IN-3 (IN-3, 4  $\mu$ M). Cells were counted after 24, 48, and 72 h of treatment and at 24 and 72 h after end of treatment (EOT). Flow cytometry, immunofluorescence microscopy, Annexin-V staining and TUNEL assay were used to detect alterations in cell cycle and apoptosis after 72 h of treatment. The TTFields/IN-3 combination decreased cell proliferation after 72 h compared to either treatment alone ( $-78.6\%$  vs. TTFields,  $P = 0.0337$ ;  $-52.6\%$  vs. IN-3,  $P = 0.0205$ ), and reduced the number of viable cells (62% less than seeded). There was a significant cell cycle shift from G1 to G2/M phase ( $P < 0.0001$ ). The apoptotic rate increased to 44% (TTFields 14%,  $P = 0.0002$ ; IN-3 4%,  $P < 0.0001$ ). Cell growth recovered 24 h after EOT with TTFields and IN-3 alone, but the combination led to further decrease by 92% at 72 h EOT if IN-3 treatment was continued ( $P = 0.0288$ ). The combination of TTFields and SAC inhibition led to earlier and prolonged effects that significantly augmented the efficacy of TTFields and highlights a potential new targeted multimodal treatment for GBM.

## Introduction

Malignant gliomas are the most prevalent, highly aggressive, invasive, and difficult to treat primary brain tumors in adults. The standard treatment regimen for patients with glioblastoma multiforme (GBM), a World Health Organization (WHO) grade IV glioma<sup>1</sup>, includes microsurgical tumor resection followed by local radiation and chemotherapy with temozolomide<sup>2,3</sup>. However, in spite of this multimodal approach the prognosis is unfavorable with a median overall survival (OS) of around 16 months, a progression-free survival of 6.9 months and a 5-year survival of only 9.8%<sup>4,5</sup>. This is accompanied by

severe deteriorations of the patients' neurological and general conditions that impair their quality of life (QoL). Therefore, more efficient treatment options with lower side effects are urgently needed to improve the outcome of patients.

Tumor treating fields (TTFields) at 200 kHz are a novel approved GBM treatment modality that demonstrated an improved median OS by 4.9 months in newly diagnosed GBM patients with only minor side effects in a clinical phase III trial<sup>6</sup> and no deterioration in QoL<sup>7,8</sup>. These alternating electric fields have a frequency range of 100–300 kHz and a field intensity of 1–3 V/cm. For clinical use they are applied at tumor specific frequencies via ceramic electrodes, so-called transducer arrays, adhered to the shaved scalp of the patient. The therapy compliance was tightly linked to the outcome and

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monthly compliance above 75% was associated with higher overall survival<sup>9,10</sup>. In addition, this important development in the treatment of GBM patients, the therapy may be further improved by its combination with synergistic therapies. To identify new facilitating compounds, we had a deeper look into the TTFields' mode of action. TTFields interfere with mitotic processes of cells on subcellular level by inhibition of spindle fiber formation and influencing other dipole macromolecules essential for cell division such as septins, ultimately leading to mitotic catastrophe, which could culminate in cell death<sup>11,12</sup>. Further affected biological mechanisms involve apoptosis, autophagy, DNA repair, and immunogenic cell death<sup>11–13</sup>.

Recently, we showed that the inhibition of the spindle assembly checkpoint (SAC) by a crucial SAC regulator, i.e., the evolutionary conserved protein kinase monopolar spindle 1 (MPS-1, also known as TTK)<sup>14</sup>, efficiently reduces GBM cell proliferation in combination with a spindle toxin<sup>15</sup>. The SAC controls the fidelity of bipolar sister chromatid attachment to functional spindle microtubules, alignment of chromosomes at the metaphase plate and presence of spindle fiber tension to ensure equal sister chromatid segregation to daughter cells during mitosis<sup>16</sup>. Defects in these processes are detected by the SAC, which initiates a mitotic cell cycle arrest by blocking the progression of metaphase to anaphase<sup>16</sup>. A defective SAC results in chromosomal instability, aneuploidy and subsequent tumorigenesis<sup>17</sup>. However, in combination with spindle fiber damaging agents like the chemotherapeutic vincristine, it accelerates mitotic catastrophe, causes cell death and even leads to shrinkage of GBM tumors in a mouse model<sup>15</sup>. Therefore, it sensitizes GBM cells to the effects of antimitotic drugs and we hypothesized that the antimitotic effects of TTFields, partially mediated by disruption of the spindle apparatus, may be facilitated and enhanced by an inhibition of the SAC regulator MPS-1. Here, we investigated if the efficacy of TTFields would be augmented by a combination of TTFields that physically damage the spindle apparatus and chemical inhibition of the SAC, leading to earlier and prolonged effects.

## Results

### TTFields impair cell proliferation most efficiently at 200 kHz in various human glioblastoma cell lines

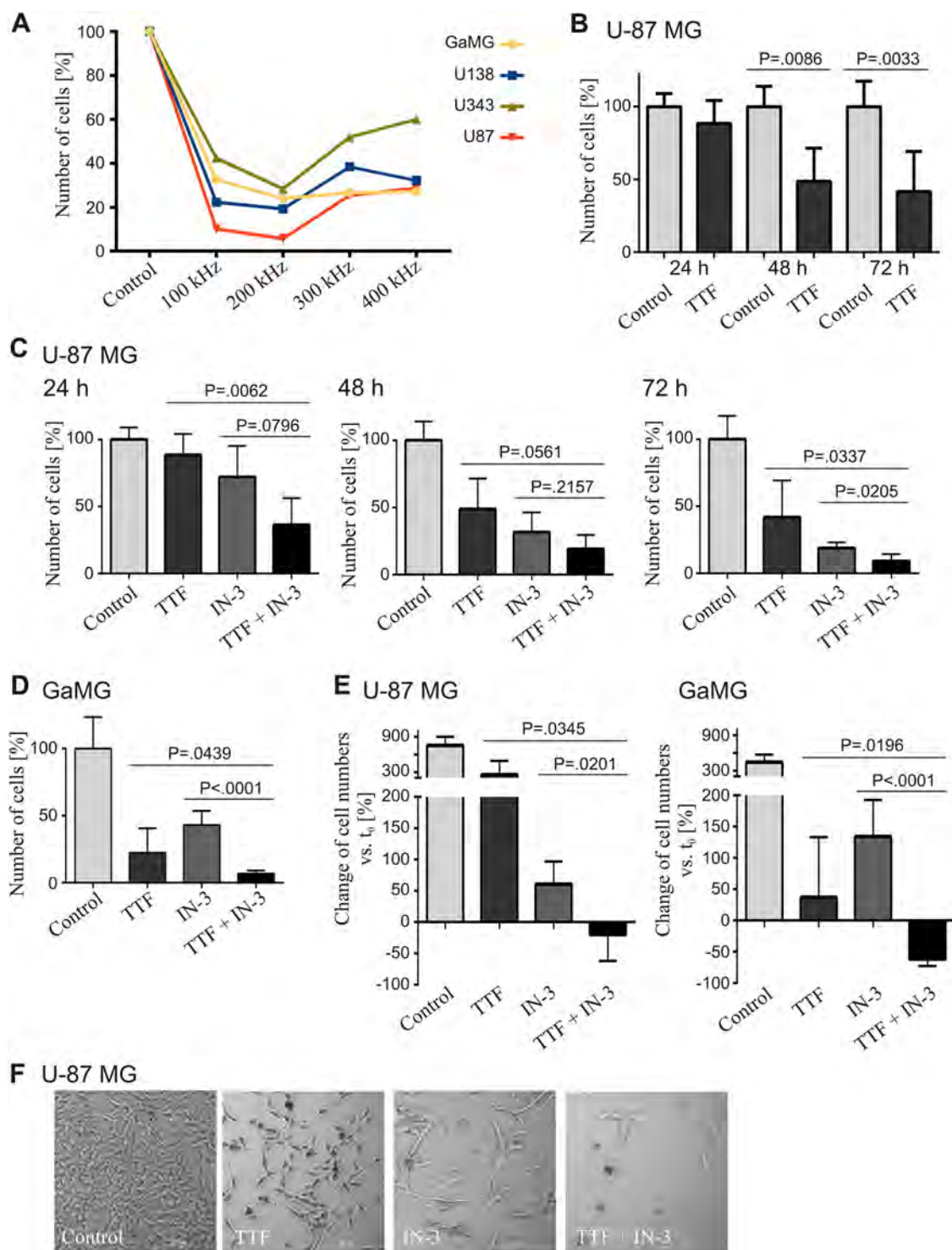
The TTFields frequency necessary to inhibit cell proliferation and to induce cell death is cell size-specific<sup>11,18</sup>. For GBM cells, a frequency of 200 kHz has been established and is applied in the clinical setting<sup>11</sup>. To reproduce these findings and to establish the in vitro technique in the laboratory, frequencies of 100, 200, 300, and 400 kHz were applied for 72 h to the four different human GBM cell lines GaMG, U-138 MG, U-343 MG, and U-87 MG

grown as monolayers on coverslips. Compared to untreated control cells, all tested cell lines responded with a significant reduction in cell proliferation at all analyzed TTFields frequencies, as estimated by cell counts (Fig. 1a). The maximum effect on cell proliferation was observed at 200 kHz, which is in line with previously published data<sup>11,12,18</sup>. Therefore, we proceeded at this specific frequency in all following experiments. U-87 MG cells were treated with TTFields for 24, 48, and 72 h. While there was no effect after 24 h, compared to the control, we observed significantly reduced cell numbers after 48 h (49%,  $P = 0.0086$ ) and 72 h (42%,  $P = 0.0033$ ), respectively, indicating a clear inhibitory effect of TTFields on proliferation (Fig. 1b, Supplementary Fig. 1A).

### The antiproliferative effect of TTFields is enhanced by SAC inhibition

Recently, we developed the SAC inhibitor MPS1-IN-3 (IN-3) and showed that it augments the efficacy of the microtubule destabilizer vincristine<sup>15</sup>. We hypothesized that we could achieve a comparable effect by combining IN-3 with TTFields, because one mechanism by which TTFields disrupts cell division is through the inhibition of spindle fiber formation. Therefore, U-87 MG cells were treated with IN-3, TTFields, or TTFields in combination with IN-3. Cells were counted after 24, 48, and 72 h (Fig. 1c, Supplementary Fig. 1C). There was no effect on cell numbers with TTFields and IN-3 alone after 24 h but an immediate and strong impact was with the TTFields/IN-3 combination. After 48 h of single treatment with IN-3 or TTFields, cell numbers were reduced to 49% ( $P = 0.0087$ , TTFields) and 32% ( $P = 0.0005$ , IN-3), respectively. The combination further decreased the cell numbers to 19% ( $P < 0.0001$ ), each compared to the control. The cell number decrease culminated after 72 h at 9% in the combination compared to TTFields alone (42%,  $P = 0.0337$ ) and to IN-3 alone (19%,  $P = 0.0205$ ) (Fig. 1c, Supplementary Fig. 1C). Similar results were obtained for GaMG cells after 72 h treatment. Compared to TTFields alone, the combined treatment reduced GaMG cell numbers by 69% ( $P = 0.0439$ ) and compared to IN-3 by 84% ( $P \leq 0.0001$ ) (Fig. 1d, Supplementary Fig. 1B). When compared to the 30,000 cells initially seeded, after 72 h U-87 MG control cells on average grew by 754%, while the single treatments grew 256% (TTFields) and 61% (IN-3), respectively (Fig. 1e, left). GaMG displayed similar proliferation with 446% (control), 37% (TTFields), and 135% (IN-3), respectively (Fig. 1e, right). Interestingly, in the combination treatment U-87 MG cell numbers were 19% (Fig. 1e, left) and GaMG cell numbers were 62% lower than the seeded cell numbers (Fig. 1e, right), indicating an even net tumor cell reduction by combining SAC inhibition with TTFields application. This was also confirmed by phase contrast





**Fig. 1** TTFields have antiproliferative effects, which are enhanced by mitotic checkpoint inhibition. Cells were treated with TTFields (TTF) and 4  $\mu$ M of the MPS1 inhibitor MPS1-IN-3 (IN-3) either alone or in combination as indicated. **a** Determination of the optimal TTFields frequency for treatment of GBM cell lines in vitro. TTFields were applied for 72 h and the cells counted ( $n = 1$ ). Totally, 200 kHz appeared to be the optimal frequency and was used for all further experiments. **b** Effect of TTFields (200 kHz) on U-87 MG cell numbers after 24, 48, and 72 h treatment. **c** U-87 MG cell numbers after 24, 48, and 72 h and **(d)** GaMG cell numbers after 72 h single and combined treatments as indicated. **e** Percentage change of U-87 MG (left) and GaMG (right) cell numbers after 72 h treatment compared to the 30,000 cells seeded at  $t_0$ . **f** Phase contrast microscopy of U-87 MG cells after 72 h treatment (representative image of  $n = 3$ ). If not otherwise stated,  $n \geq 3$  independently repeated experiments were performed. SD is shown as error bars



microscopy of U-87 MG cells. In addition to changes in cell numbers, the treated cells appeared to be enlarged and showed an altered phenotype especially in the combination treatment (Fig. 1f).

#### **TTFields in combination with IN-3 causes accumulation of nuclear abnormalities, affects cell cycle and increases apoptosis**

TTFields have been shown to disrupt mitosis and to increase abnormal mitotic figures<sup>11,18</sup>. Indeed, we observed very distinct mitotic figures, especially with the combined treatment, with multipolar spindles and massive chromosomal missegregation in GaMG cells (Fig. 2a). Subsequently, these disturbances lead to abnormal chromosome distribution, aneuploidy, and dysmorphic nuclei, as reported for both TTFields and IN-3<sup>15,19</sup>. Therefore, we quantified the number of abnormal nuclei in U-87 MG cells from the different treatment groups after 72 h (Fig. 2b). Both single treatments significantly increased the numbers of aberrant nuclei (TTFields: 38% and IN-3: 64%, both  $P < 0.0001$ ) compared to the control (9%). The combined treatment led to the highest percentile of abnormal nuclei (73%), which was significantly higher than either treatment alone ( $P = 0.0002$  vs. TTFields and  $P < 0.0001$  vs. IN-3) (Fig. 2b). Further characterization of the cell cycle by FACS analyses clearly showed that the combination of TTFields with IN-3 caused a cell-cycle shift from mainly G1 to the G2/M-phase beyond the effects of the single treatment in U-87 MG (Fig. 2c) and GaMG cells (Supplementary Fig. 1D). In addition, a significant increase of sub-G1 cells was detectable, which most likely were dead cells subject to apoptosis (Fig. 2c, Supplementary Fig. 1D). The combination treatment of TTFields plus IN-3 induced an early stage of apoptosis in 44% of U-87 MG cells, compared to 14% with TTFields alone ( $P = 0.0002$ ), and 4% with IN-3 alone ( $P < 0.0001$ ) (Fig. 3a). These data were confirmed by the TUNEL assay (Fig. 3b), and clearly showed that the inhibition of the SAC can considerably increase the effects of TTFields by enforcing cell death.

#### **SAC inhibition can bridge the interruption of TTFields treatment**

The combination of TTFields and IN-3 showed a more pronounced effect on cell proliferation (Fig. 1c), viability (Fig. 1e), the ratio of dead/alive cells (Fig. 2c), and an increased apoptotic rate (Fig. 3) compared to the single treatments. An inevitable question is the sustainability of the applied treatments, especially whether the strong impact of the combination would translate into persistent and long-lasting effects. Therefore, we evaluated cell numbers after 72 h of exclusive TTFields treatment. Subsequently, the treatment was discontinued (end of treatment, EOT) and the cells proliferation observed for

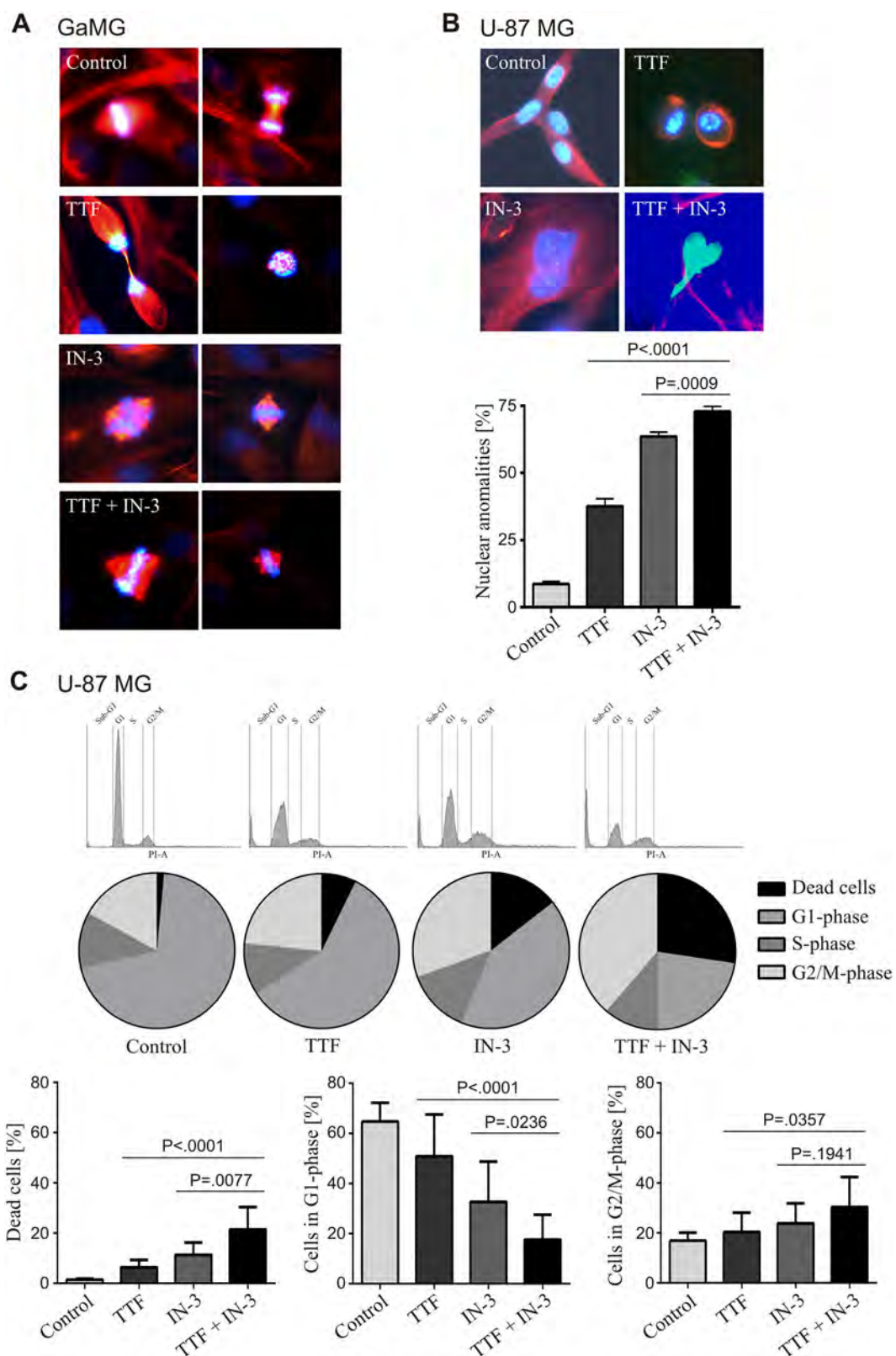
another 24 and 72 h (Fig. 4a). Following EOT, cell numbers decreased significantly to 46% ( $P = 0.0400$ ) during the next 24 h. However, 72 h after EOT the cells had recovered and restarted proliferation. For the treatment solely with IN-3 we found similar results (Fig. 4b). Continued treatment with IN-3 for 72, 96, and 144 h led to a considerably reduced cell number to 59% ( $P = 0.0042$ ), whereas a discontinuation of the IN-3 treatment after 72 h did not cause a further decrease of cells. Surprisingly, continuation of IN-3 treatment after 72 h of combined TTFields plus IN-3 treatment for another 24 and 72 h induced a further reduction of cell numbers down to 8% ( $P = 0.0288$ ). Notably, this effect was stronger than the effect of IN-3 that was given permanently to the cells reflecting a synergism with the clonogenic effect of TTFields even after discontinuation of the latter treatment (Fig. 4c).

#### **Discussion**

GBM therapy urgently needs new treatment approaches that will improve overall survival, while preserving patients' QoL. TTFields are a new therapy approved by the FDA for newly diagnosed and recurrent GBM and are considered a fourth treatment modality that improves overall survival with a minimal impact on patients QoL<sup>6–8</sup>. In the clinical setting, an optimal frequency of 200 kHz has been established for the treatment of GBM, which is in accordance with previously published<sup>11,12,18</sup> as well as our own data derived from cell culture experiments that show that GaMG cells are more sensitive to TTFields than U87-MG cells. The primary mechanism of action for TTFields is the disruption of the normal spindle microtubule assembly by decreasing the ratio between polymerized and total tubulin<sup>12</sup>. Such spindle fiber damage usually activates the SAC and induces cell cycle arrest in the G2/M-phase until the spindle defect is resolved<sup>16</sup>. Prolonged induction of the SAC is the means by which established, chemical microtubule poisons in cancer therapies such as vinca-alkaloids or taxanes work. Prolonged metaphase arrest often causes apoptotic cell death<sup>20–22</sup>. However, one major problem of such therapeutic interventions is that SAC activation and metaphase arrest are not permanent. Cells can escape by a mechanism called mitotic slippage, a mitotic exit without cytokinesis, leading to tetraploid cells. The fate of these cells can be post-slippage cell death by mitotic catastrophe or during a G1-arrest by senescence. Some cells, however, resume proliferation and become aneuploid<sup>23,24</sup>.

Treating cancer cells with TTFields led to an increase of mitotic apoptosis, nuclear abnormalities like polynucleation, micronucleation, and autophagy<sup>12,13</sup>, which are all hallmarks of mitotic catastrophe<sup>23</sup>. These effects were confirmed in our experiments when applying TTFields to GBM cell lines. However, our main objective was to





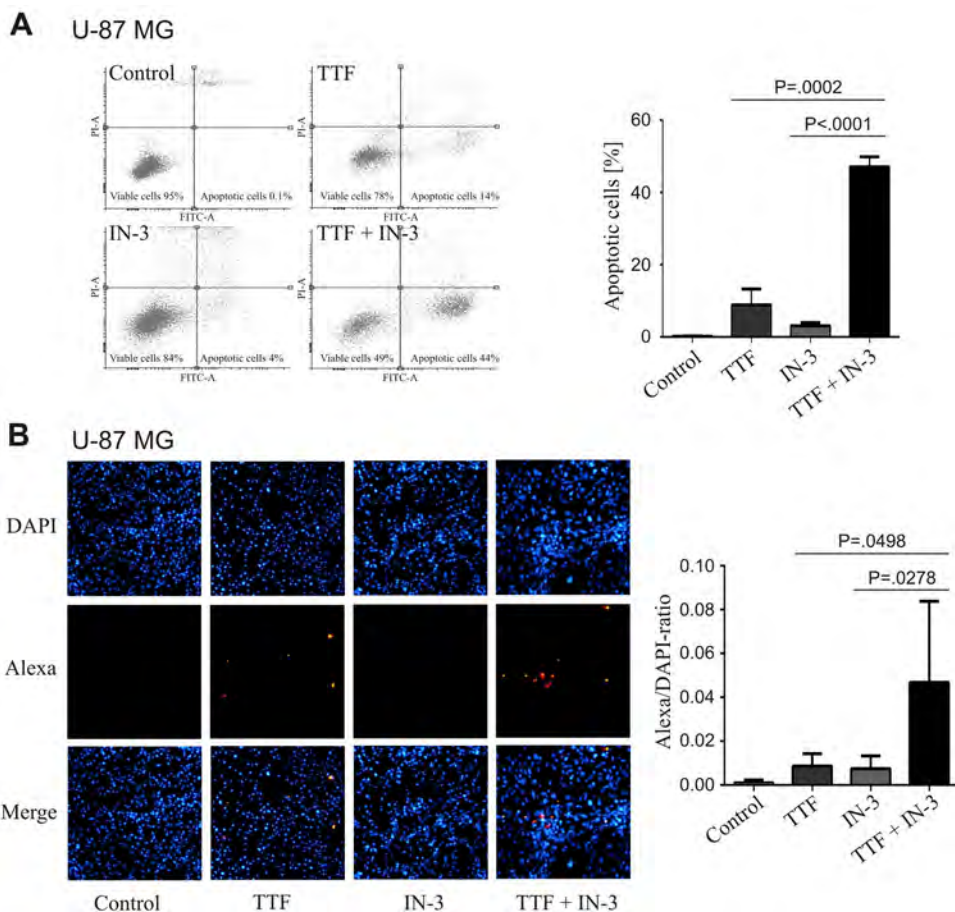
**Fig. 2** (See legend on next page.)



(see figure on previous page)

**Fig. 2** TTFields in combination with MPS1-inhibition affect the cell cycle and cause multipolar spindles and chromosomal missegregation.

**a** Representative fluorescence images of typical mitotic figures of GaMG cells. The different treatments are indicated. Blue: DAPI, green:  $\gamma$ -tubulin, red:  $\alpha$ -tubulin. **b** Representative fluorescence images of nuclear abnormalities (top) and their quantification (bottom) of U-87 MG cells. A total of  $n = 3$  independent experiments were performed and of each experiment 100 nuclei were counted per treatment group. **c** Distribution of U-87 MG cells to the different cell cycle phases measured by FACS analysis (PI-staining). Histograms (top), average percentage distribution (middle) and percentage of cells in the sub-G1- (dead cells), G1- and G2/M-phase of the cell cycle are shown ( $n = 12$ ). SD is shown as error bars



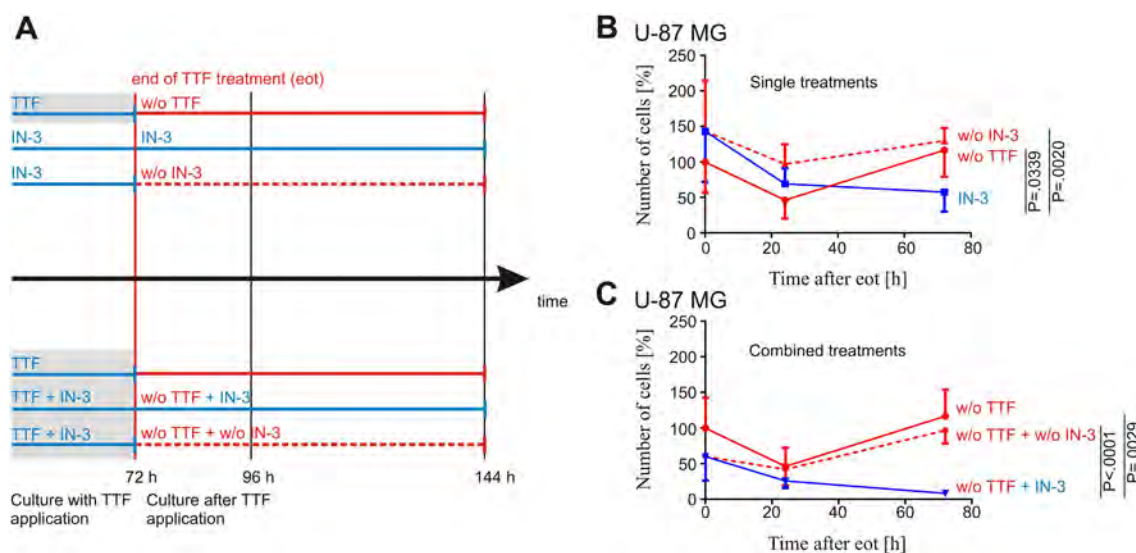
**Fig. 3** Increase of apoptotic cell death by the combined treatment with TTFields and IN-3 of U-87 MG cells. **a** FACS analysis of U-87 MG cells' early apoptosis as measured by Annexin V staining after 72 h treatment as indicated. Representative histograms (left) and their quantification (right) are shown ( $n = 3$ ). **b** Alexa-TUNEL assay of U-87 MG cells in situ to detect late apoptosis after 72 h treatment. Representative fluorescence images (left) and their quantification (right) are presented ( $n = 6$ ). SD is shown as error bars

further improve the treatment efficacy of TTFields by facilitating and enhancing their spindle disrupting effect. This objective was based on our recent observation that inhibition of the SAC key regulator MPS1 by a newly developed inhibitor MPS1-IN-3 (IN-3) in conjunction with the application of the spindle poison vincristine resulted in significantly less cell cycle arrest, and drastic nuclear aberrations, including lobed nuclei, multi-nucleated cells and micronuclei, which reflect gross chromosome segregation defects. In addition, the

combination of IN-3 and vincristine led to almost complete tumor shrinkage and prolonged survival in orthotopic GBM mouse models<sup>15</sup>. Therefore, we concluded that selective MPS1 inhibition sensitizes GBM cells to the effects of antimitotic drugs, an assumption supported by data reported by other groups<sup>25–28</sup>.

Indeed, our data provide evidence that a combination of MPS1 inhibition and TTFields treatment of GBM cells elicited more than just additive effects. The anti-proliferative benefit of the combination treatment started





**Fig. 4** SAC inhibition prolongates TTFields-effects in U-87 MG cells. **a** Experimental scheme. Application of TTFields (gray background) and IN-3 is indicated in blue and was maintained either alone or in combination for 72 h. TTFields application was ended (EOT red) and cells cultured for another 72 h either with (IN-3, blue) or without (w/o IN-3, red, dotted line) IN-3. Cells were counted after 72, 96, and 144 h overall culture, as indicated. **b** TTFields were applied to U-87 MG cells for 72 h and then switched off. The cells' proliferation was determined by cell counting at treatment end (0 h, 100%), and 24 and 72 h after end of TTFields application (w/o TTF, red). U-87 MG cells were incubated with 4  $\mu$ M IN-3 for 72, 96, and 144 h (IN-3, blue) and counted or incubated with IN-3 for 72 h, further cultivated for 24 and 72 h without IN-3 (w/o IN-3, red, dotted line) and then counted. **c** For combined treatment, TTFields were applied to U-87 MG cells for 72 h and then switched off (w/o TTF, red), while 4  $\mu$ M IN-3 was present for 72, 96, and 144 h, respectively (IN-3, blue) or cells were cultured for 72 h with TTFields and 4  $\mu$ M IN-3 and then TTFields were switched off and IN-3 was removed, while the cells were further cultivated for 24 and 72 h after end of treatment (red, dotted line). Experiments were independently repeated with  $n \geq 3$ . SD is shown as error bars

after 24 h, while the single treatments only began to be effective after 48 h. This reflects an acceleration of the comparably slow effect of TTFields action, which is dependent on the direction of the cell axis and the cell division rate<sup>11,12,18</sup>. Importantly, the combination treatment was the only one causing a net reduction of cells below the seeded cell number, while all other treatments only throttled cell proliferation. Whereas the latter findings were in line with published data on TTFields<sup>11,18</sup> and MPS1 inhibitors<sup>29,30</sup>, the former discovery is a novel finding indicating that the combination may increase cell death by mitotic catastrophe, an assumption confirmed by cell cycle analysis, immunofluorescence imaging and apoptosis assays. Thus, these findings may open new perspectives for the treatment of GBM patients by augmenting the TTFields efficacy.

The compliance with TTFields therapy in the clinical trials was tightly linked to the survival outcomes; monthly compliance above 75% was associated with higher overall survival<sup>9,10,31</sup>. Our cell culture experiments revealed that the surviving cells recover with a delay of 24 h after end of TTFields application. This observation suggests that interruption of TTFields treatment for 24 h may still be bridged by the repercussion of the therapy<sup>11</sup>, whereas a treatment break of more than 24 h would result in resumed tumor growth. Therefore, longer treatment breaks should be

avoided to allow optimal clinical outcome. Nevertheless, there are circumstances that inevitably lead to discontinuation of the therapy, e.g., skin irritations<sup>32,33</sup>. It would be of clinical importance to determine if such treatment breaks could be bypassed. After treatment with TTFields and IN-3 for 72 h the cell numbers further decreased considerably at 72 h after terminating TTFields application, indicating a persisting effect when applying the MPS-1 inhibitor. Therefore, such a combination could potentially bridge short breaks and ease the everyday life of patients at same or even better efficacy.

Taken together, the combination of TTFields with the chemical inhibition of SAC was able to reduce GBM cell proliferation, increase apoptosis and could potentially serve as a bridge for TTFields therapy interruption in the clinical setting. Recently, several potent MPS1 inhibitors have been developed<sup>26,34–36</sup> and two of them, BAY1161909 and BAY1217389, are currently in phase I clinical trials<sup>27,37</sup>. Our data provide a rationale for the future clinical evaluation of combined therapies utilizing TTFields and MPS1 inhibitors in patients with GBM.

## Materials and methods

### Cell lines, cell culture and TTFields application

The human GBM cell lines U-87 MG, U-138 MG, and U-343 MG were purchased from Cell Lines Service (CLS,



Eppelheim, Germany). The cell line GaMG was obtained from the Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Cultures (DSMZ, Braunschweig, Germany). Cells were grown as reported elsewhere<sup>38</sup> in 75 cm<sup>2</sup> flasks (Corning, New York, NY, USA) at 37 °C in an atmosphere of 5.0% CO<sub>2</sub> and 100% humidity.

Novocure's *in vitro*<sup>TM</sup> laboratory research system for the treatment of cancer cells was used to administer TTFields to GBM cells *in vitro* as described by Porat et al.<sup>39</sup>. In brief, 24 h before start of TTFields application, cells were trypsinized and plated by placing 350 µl medium containing 30,000 cells as a drop in the center of a glass coverslip (20 mm in diameter) (Hartenstein, Würzburg, Germany) within an *in vitro* ceramic dish (Novocure, Haifa, Israel). After 20 h incubation at 37 °C and 5.0% CO<sub>2</sub> to allow the cells' adhesion, the medium was removed and the plates were filled with 2 ml fresh medium and 2 ml medium containing 4 µM of MPS1-IN-3 (IN-3) (Sigma-Aldrich, St. Louis, MO, USA), respectively. The ceramic dishes were placed onto a base plate connected to a TTFields generator. Each ceramic dish contains two pairs of electrodes perpendicular to each other. A sinusoid function generator and an amplifier integrated into the *in vitro* system generate alternating electric fields<sup>13</sup>. The medium was renewed every 48 h.

#### Cell counting

TTFields were applied for up to 72 h. To evaluate their effects, cells were trypsinized after 24, 48, and 72 h of TTFields application as well as 24 and 72 h after ending TTFields treatment (EOT) by removing the medium, washing with phosphate-buffered saline (PBS) (Biochrom, Berlin, Germany) and adding 0.5 ml Trypsin/EDTA solution (Gibco, Eggenstein, Germany)<sup>39</sup>. The reaction was stopped by adding 1 ml of medium to each plate and cells were counted utilizing the Scepter 2.1 cell counter (Merck, Darmstadt, Germany).

#### Fluorescence immunocytochemistry

Cells grown on coverslips were washed with PBS and fixed in 4% (vol/vol) paraformaldehyde (Merck, Darmstadt, Germany) in PBS for 30 min at room temperature. Cells were rinsed three times with 70 µl TBST (50 mM Tris (Roth, Karlsruhe, Germany), 150 mM NaCl (Merck, Darmstadt, Germany), pH 8.0, 0.5% (vol/vol) Tween-20 (Sigma-Aldrich, St. Louis, MO, USA)) permeabilized and blocked in 70 µl blocking solution (10% (vol/vol) goat serum (Jackson, West Baltimore Pike, USA), 1% (wt/vol) BSA (Serva, Heidelberg, Germany), 0.05% (vol/vol) Triton-X 100 (Sigma-Aldrich, St. Louis, MO, USA) in PBS) for 30 min at room temperature. Totally, 70 µl primary antibody mixture of rabbit anti  $\gamma$ -tubulin diluted 1:1000 and mouse anti  $\alpha$ -tubulin diluted 1:2000 (both from Sigma-Aldrich, St. Louis, MO, USA) in 1% (wt/vol)

BSA, 0.05% (vol/vol) Triton-X 100 in PBS, were added to each cover slip and incubated over night at 4 °C for immunocytochemistry. The cells were washed three times with 70 µl TBST and blocked for 30 min at room temperature in 70 µl blocking solution before they were incubated in the dark with the secondary antibody mixture Cy2-goat-anti rabbit diluted 1:50 and Cy3-goat-anti mouse (both from Jackson, West Baltimore Pike, USA) diluted 1:100 in 1% BSA, 0.05% Triton-X 100 in PBS. After 2 h incubation at room temperature cells were washed three times with 70 µl TBST. Cover slips were mounted to glass slides using fluoromount aqueous mounting medium containing DAPI (Sigma-Aldrich, St. Louis, MO, USA), dried over night at room temperature and stored for 24–48 h at 4 °C. Cells were viewed on an inverted fluorescence microscope LEICA DMI 3000 B. 100 nuclei of each treatment group were inspected and the ratio of aberrant to normal nuclei was calculated. Images were captured through a 100× objective by using the LEICA DFC450 camera and LAS V4.5 software (all Leica, Wetzlar, Germany).

#### Cell cycle analysis and apoptosis assays

After 72 h of TTFields treatment, floating cells from the medium were harvested by centrifugation at 230×g and adherent cells were dissolved by trypsinization. Both cell populations were washed once with 5 ml ice cold PBS, combined and finally resuspended in 500 µl PBS.

For cell cycle analysis the cells were fixed in 4 ml ice cold 70% ethanol (J. T. Baker, Deventer, The Netherlands) and stained with propidium iodide (Sigma-Aldrich, St. Louis, MO, USA). Analysis of the DNA content was performed by flow cytometry (BD FACS Canto 2.0, Becton-Dickinson, Franklin Lakes, NJ, USA) and evaluated with Flowing Software 2.5.1 (University of Turku, Finland).

To measure cell death by Annexin V staining, PBS-washed cells were incubated for 15 min in 500 µl binding buffer (0.01 M HEPES pH 7.4 (Roth, Karlsruhe, Germany), 0.14 M NaCl, 2.5 mM CaCl<sub>2</sub> (both from Merck, Darmstadt, Germany) in PBS), 10 µl propidium iodide (Sigma-Aldrich, St. Louis, MO, USA) and 5 µl FITC-Annexin (Becton-Dickinson, Franklin Lakes, NJ, USA), at room temperature. Within 1 h measurements were performed by flow cytometry (BD FACS Canto 2.0, Becton-Dickinson, Franklin Lakes, NJ, USA). For cell death analysis by TUNEL assay, ethanol fixed cells were stained using the TUNEL Assay Kit—In situ Direct DNA Fragmentation (Abcam, Cambridge, UK) according to the manufacturers protocol. Photographs of stained cells were taken using the LEICA DFC450 camera mounted to a LEICA DMI 3000 B fluorescence microscope and LAS V4.5 software (all from Leica, Wetzlar, Germany). Apoptosis was quantified by counting DAPI and Alexa stained cells using ImageJ<sup>40</sup> and calculating the DAPI/Alexa ratio.



## Statistical analysis

All experiments have been repeated independently at least three times, except for the test of the optimal TTFields frequency, which has been done only once as a proof of already published data<sup>11,12,18</sup>. Statistical analysis was performed using GraphPad Prism 6 Software (GraphPad Software Inc., San Diego, USA). Statistical significance was defined by unpaired two tailed Student's *t* tests and ANOVA, as applicable. *P* < 0.05 was considered to be significant.

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## Conflict of interest

The authors declare that they have no conflict of interest.

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## CNS CANCER

## TTFields improve survival

Glioblastoma is the most common and aggressive form of primary brain tumour, with median overall survival durations in clinical trials of <17 months emphasizing the need for more effective therapy. In 2015, promising interim results of a phase III trial were reported for a novel non-invasive, non-pharmacological treatment modality termed tumour-treating fields (TTFields). The final results have now been published.

TTFields involves the continuous delivery of low-intensity, intermediate-frequency (200 kHz) alternating electrical fields to the tumour using a portable generator connected to a transducer cap worn on the patient's scalp. These electrical fields have been shown to cause mitotic arrest, disrupt organelles, and induce apoptosis selectively in rapidly dividing cells, such as glioblastoma cells.

In the trial, 695 patients who had undergone surgery for glioblastoma followed by concomitant chemoradiotherapy were randomly assigned (2:1) to receive TTFields plus temozolomide or maintenance temozolomide alone. Uninterrupted use of the TTFields device for  $\geq 18$  h per day was recommended and could be continued until second radiographical progression, together with second-line therapy (which in both arms was offered per local practice).

The median progression-free survival from randomization was 6.7 months with TTFields versus 4 months with temozolomide alone (HR 0.63;  $P < 0.001$ ). Moreover, overall survival was also improved by addition of TTFields to maintenance therapy: median 20.9 months versus 16 months (HR 0.63;  $P < 0.001$ ). In an exploratory analysis, 5-year overall survival was 13% versus 5% ( $P < 0.004$ ). Of note, the baseline patient characteristics, including MGMT-promoter methylation status (which correlates with the effectiveness of temozolomide), were well balanced between the treatment arms; TTFields was associated with longer survival in all *post hoc* subgroups.

Importantly, this treatment approach seemed to be well tolerated by patients, and the profile and frequency of adverse events were similar in both treatment arms. However, localized skin toxicities were observed only with TTFields, at the device site (52% grade 1–2, 2% grade 3). Together, these findings support the utility and safety of TTFields in the treatment of glioblastoma.

David Killock

**ORIGINAL ARTICLE** Stupp, R. *et al.* Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *JAMA* **318**, 2306–2316 (2017)



# Beyond the chemotherapy for brain tumor treatment in neuro-oncology practice

Xiao-Tang Kong\*

Kong. Beyond the chemotherapy for brain tumor in neuro-oncology practice. J Neurol Clin Neurosci. Oct 2018;2(3):16.

## Are Neurologists Ready to See the Patients wearing Optune Electric Cap?

Glioblastoma (GBM) is the most malignant brain tumor in adults. Since 2005, newly diagnosed GBM has been treated with surgery, radiation and adjuvant chemotherapy with temozolomide [1]. The standard therapy applied by neuro-oncologists for GBM patients is to provide the chemotherapy agent called temozolomide, to manage seizures and other complications from treatment and disease. With the above aggressive treatment, newly diagnosed GBM has only had a limited median overall survival time of 14.6 months. In 2011, the FDA approved the tumor-treating fields (TTFields) device, Optune (also called Novo TTF) for recurrent GBM [2] after the study showed a non-inferior effect of Optune to “best standard chemotherapy” chosen by doctors. Optune is a portable, battery-operated device that generates electric fields and is worn by the patients on their head like a cap for the treatment of supratentorial brain tumor. Some patients call it an “Electric Cap.” The mechanism is to produce alternating electric fields to interfere with highly charged macromolecules and organelles in rapidly dividing cancer cells to disrupt their neat alignment during the phase of mitosis.

In 2015, FDA approved Optune for newly diagnosed GBM after an EF-14 clinical trial found a positive outcome for patients with brain cancer [3]. In 2017, Optune became part of the NCCN guidelines in the treatment of newly diagnosed GBM [NCCN Guidelines®] [4]. The trial randomized 695 patients with a 2:1 ratio of Optune arm (446) to control arm (229). Both arms were treated with concurrent chemotherapy and radiation therapy followed by adjuvant chemotherapy. Then the trial arm wore the device Optune on head and received adjuvant chemotherapy while the control group only received adjuvant chemotherapy. With the addition of Optune to chemotherapy for newly diagnosed malignant GBM, the overall survival time increased to more than 20 months [2]. Of particular note, the five-year survival rate increased from approximately 5 % to 10% [5]. Because of the EF-14 study, an increasing number of neuro-oncologists have started prescribing Optune for the treatment of GBM in addition to standard chemotherapy.

More GBM patients may be seen wearing this device on their heads and visiting neurologists of various subspecialties. First, the patient wearing Optune may present to neurologists with a variety of neurological issues just like patients without brain tumors. Second, the patients wearing

Optune may have complications from the tumor itself and treatment related complications such as seizure, headache, nausea, vomiting, focal or generalized weakness, fatigue, or stroke, for which they search for general neurology care because there may be no neuro-oncology service in their local area. Third, the patients may develop adverse effects from Optune.

The adverse effects of Optune are less compared to systemic chemotherapy. The major side effect is focal scalp irritation. Other uncommon side effects including headache, seizure, anxiety, depression, fatigue and insomnia, which might or might not be related to Optune since the trial found no statistical difference between the Optune trial group and the control group [2]. Health related quality of life is maintained [6]. For scalp irritation, the treatments include application of local steroid lotion or cream, and antibiotics ointment if needed. Patients are also allowed to wear Optune when they undergo a CT head study though are not allowed to wear it during a brain MRI study.

As neurologists, we need to be familiar with the concepts of the Optune treatment, the device itself and how to manage the potential side effects of the device when patients wearing Optune “Electric Cap” come to see us for management of their neurological issues.

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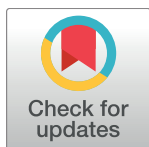
RESEARCH ARTICLE

# Importance of electrode position for the distribution of tumor treating fields (TTFields) in a human brain. Identification of effective layouts through systematic analysis of array positions for multiple tumor locations

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## Abstract

Tumor treating fields (TTFields) is a new modality used for the treatment of glioblastoma. It is based on antineoplastic low-intensity electric fields induced by two pairs of electrode arrays placed on the patient's scalp. The layout of the arrays greatly impacts the intensity (dose) of TTFields in the pathology. The present study systematically characterizes the impact of array position on the TTFields distribution calculated in a realistic human head model using finite element methods. We investigate systematic rotations of arrays around a central craniocaudal axis of the head and identify optimal layouts for a large range of (nineteen) different frontoparietal tumor positions. In addition, we present comprehensive graphical representations and animations to support the users' understanding of TTFields. For most tumors, we identified two optimal array positions. These positions varied with the translation of the tumor in the anterior-posterior direction but not in the left-right direction. The two optimal directions were oriented approximately orthogonally and when combining two pairs of orthogonal arrays, equivalent to clinical TTFields therapy, we correspondingly found a single optimum position. In most cases, an oblique layout with the fields oriented at forty-five degrees to the sagittal plane was superior to the commonly used anterior-posterior and left-right combinations of arrays. The oblique configuration may be used as an effective and viable configuration for most frontoparietal tumors. Our results may be applied to assist clinical decision-making in various challenging situations associated with TTFields. This includes situations in which circumstances, such as therapy-induced skin rash, scar tissue or shunt therapy, etc., require layouts alternative to the prescribed. More accurate distributions should, however, be based on patient-specific models. Future work is needed to assess the robustness of the presented results towards variations in conductivity.



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## Introduction

Glioblastoma multiforme (GBM) is a devastating brain cancer with an incidence of approximately 3–4/100,000 [1]. Standard therapy includes maximal safe resection of the tumor followed by radio-chemotherapy [2–8]. In addition, tumor treating fields (TTFields) are increasingly being used as a supplementary treatment modality for both recurrent and newly diagnosed GBM [9–12]. TTFields are low intensity ( $1\pm3$  V/m) intermediate frequency (200 kHz) alternating electrical fields, which inhibit tumor growth. Clinical trials with TTFields have demonstrated promising results [13–19]. For recurrent GBM, the technology performs as well as best physicians' choice chemotherapy but is associated with far less discomfort and adverse events [13]. For newly diagnosed GBM, TTFields increase the median overall survival by approximately five months when applied in addition to standard radio-chemotherapy [14,17,19–21].

TTFields are generated by two pairs of 3x3 electrode arrays placed on the scalp of the patient so that the fields induced by each pair are presumably orthogonal. Each pair of arrays is supplied by a portable and battery-powered current source carried by the patient. The sources are activated in sequence so when one source is active, the other is inactive and vice-versa. Each source has a repeated 50% square (on/off) duty-cycle of 2 s total duration, i.e. within one duty-cycle the source is active for 1 s, and then inactive for 1 s. During activation, each source induces a 200 kHz sinusoidal alternating field and the maximum peak-to-peak current delivered is 1.8A. The current level is controlled to maintain a skin temperature below 41°C. The therapeutic benefit depends on user compliance and the device "on-time" and the device should be active for at least 18 hours per day [22] ([https://www.optune.com/content/pdfs/Optune\\_PLOM\\_8.5x11.pdf](https://www.optune.com/content/pdfs/Optune_PLOM_8.5x11.pdf)).

The mechanism of action of TTFields is believed to relate mainly to direct physical interference with the mitotic process, such as septin and tubulin assembly and also direct migration of polarized particles in dividing cells [23–25]. Previous *in vitro* studies have established a significant dependency between the intensity of the induced field and the degree of tumor growth reduction [23,24]. The lower threshold of inhibition was determined to be 100 V/m while field intensities higher than 225 V/m induced tumor regression. Given this significant dose-response relationship, it is clear that the distribution of TTFields inside the head, brain, and tumor plays an important role for the expected treatment benefit for each patient. Therefore, methods to quantify this distribution are highly warranted, and recent studies have described various approaches to achieve this goal using finite element (FE) methods [26–36]. In a recent study, MRI data from a GBM patient were used to produce an accurate head FE model allowing for precise representation of the individual anatomy and dielectric property distribution. The approach was used to investigate the potential enhancement of TTFields using craniectomy and skull remodeling surgery to create paths for current flow directly into the tumor. In another study, a head model was constructed from MRI data of a healthy individual. The model was modified to incorporate virtual pathologies by post-processing of the head mesh [36] and used to identify general factors affecting the distribution of TTFields, such as tumor position, the type of surrounding tissue, and the presence of central necrosis in the tumor.

Despite the increasing focus on understanding the biophysics of TTFields, several questions remain unanswered. In this study, we will utilize a virtual lesion FE approach similar to the one described above to systematically investigate the impact of electrode position on the TTFields distribution and the average dose of TTFields experienced by tumors spanning a large range of the hemispheric regions. We will investigate the impact of systematic rotation of the transducer array pairs around a central craniocaudal axis of the head to investigate optimal configurations and transducer array layouts for various tumor locations. As a novel and significant finding, we



will show that an oblique array layout is superior to the standard left-right (LR) and anterior-posterior (AP) array layout for many tumor locations. Furthermore, our results will provide systematic and direct visual and quantitative information on the impact of electrode movement on the TTFields distribution. This information is highly important for clinicians and users who often have to adapt TTFields therapy and electrode layout to counter common challenges, such as therapy-induced skin rash beneath the electrodes. We hope to support users and clinicians to gain a better understanding of the TTFields therapy treatment and thereby aid treatment planning and optimize the clinical implementation of the technology.

## Methods

### Field calculations

We calculated the electric field distribution in a realistic model of a human head using a finite element (FE) approximation of the electric potential [26,27,33,35±38]. In general, the quantities defining a time-varying electromagnetic field are given by the complex Maxwell equations [39]. However, in biological tissues and at the low to intermediate frequency of TTFields ( $f = 200\text{kHz}$ ), the electromagnetic wavelength is much larger than the size of the head and the electric permittivity  $\epsilon$  is negligible compared to the real-valued electric conductivity  $\sigma$ , i.e.  $\frac{\omega\epsilon}{\sigma} \ll 1$ , where  $\omega = 2\pi f$  is the angular frequency [40]. This implies that the electromagnetic propagation effects and capacitive effects in the tissue are negligible, so the scalar electric potential  $\phi$  may be well approximated by the static Laplace equation  $\nabla \cdot (\sigma \nabla \phi) = 0$ , with appropriate boundary conditions at the electrodes and skin [26,31,40,41]. Thus, the complex impedance is treated as resistive (i.e. reactance is negligible) and currents flowing within the volume conductor are, therefore, mainly free (Ohmic) currents. The validity of this approximation for TTFields has further been established by Wenger *et al.*, 2015 [31], who showed that permittivity affects the intensity of the resulting field distribution in a realistic human head model by less than 2%. Similar observations were recently made by Lok *et al.*, 2017 [33]. Therefore, we have adopted the simpler electrostatic approximation in this study. We would like to note that, while this approach is valid for the estimation of the macroscopic field distribution in the head volume conductor, capacitive effects of the cell membranes have to be taken into account when modelling the penetration of the external current flow into tumor cells on the microscopic level [30,42]. However, the latter is not the topic of this study. The FE approximation of Laplace's equation was calculated using the SimNIBS software ([www.simnibs.org](http://www.simnibs.org)) [43]. Computations were based on the Galerkin method [44] and the residuals for the conjugate gradient solver were required to be  $<1\text{E}-9$ . Dirichlet boundary conditions were used with the electric potential was set to (arbitrarily chosen) fixed values at each set of electrode arrays [45,46]. The electric (vector) field was calculated as the numerical gradient of the electric potential and the current density (vector field) was computed from the electric field using Ohm's law. The potential difference of the electric field values and the current densities were linearly rescaled to ensure a total peak-to-peak amplitude for each array pair of 1.8 A, calculated as the (numerical) surface integral of the normal current density components over all triangular surface elements on the active electrode discs. This corresponds to the current level used for clinical TTFields therapy by the Optune® device. The "dose" of TTFields was calculated as the intensity ( $L^2$  norm) of the field vectors. We assumed the modeled current to be provided by two separate and sequentially active sources each connected to a pair of 3x3 transducer arrays (see below). The left and posterior arrays were defined to be sources in the simulations, while the right and anterior arrays were the corresponding sinks, respectively. However, as TTFields employ alternating fields, this choice is arbitrary and does not influence the results.

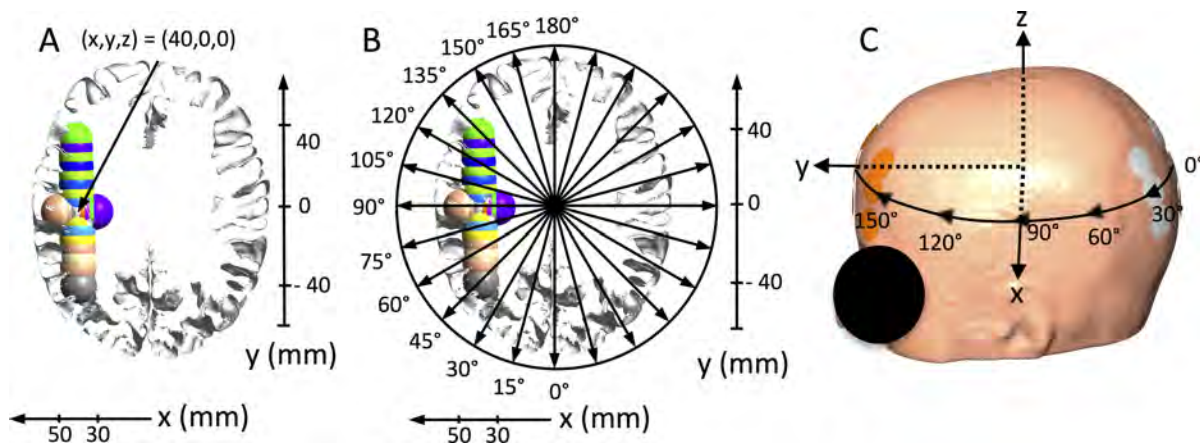


## Head model generation and positioning of tumors and arrays

A realistic head model was constructed from MRI data from a healthy individual (almi5 dataset available at [simnibs.org](http://simnibs.org)). The computational head mesh was initially segmented into skin, bone, cerebrospinal fluid (CSF), gray matter (GM) and white matter (WM). To ensure systematic positioning of tumors and electrode arrays, we defined a right-handed reference coordinate system in the model (Fig 1). We kindly refer the reader to Korshoej *et al.* (2017) for a full description of how this coordinate system was constructed [36]. In summary, a transversal plane was initially defined by conventional LR and AP positioning of the arrays. The left-right direction was defined as the x-axis, the AP direction as the y-axis, and the cranio-caudal direction normal to the xy-plane was defined as the z-axis.

After defining the coordinate system, nineteen spherical tumors were placed at systematically varying x, y and z coordinates to obtain a wide and clinically relevant range of cortical and sub-cortical tumor positions in the frontal, parietal, and occipital regions of the right hemisphere (Fig 1A). Tumor lesions were translated along the defined axes around a central position at the frontoparietal junction (corresponding to  $x = 40$  mm,  $y = 0$  mm,  $z = 0$  mm, see Fig 1). The exact tumor coordinates are stated in the caption of Fig 1 and the intersecting surfaces of all tumors are shown in Fig 1A and 1B along with corresponding x- and y-coordinate axes ( $z = 0$ ). Tumor lesions had external radii of 10 mm and inner core radii of 7 mm defining a core of central necrosis, as previously investigated by the Authors and by Miranda *et al.* [26,28,31].

Electrode arrays consisted of nine electrodes of 20 mm diameter arranged in a 3x3 array structure. The center-to-center distances between neighboring electrodes were 45 mm and 22 mm, respectively (Fig 1C). The transducer array configuration corresponded entirely to the Optune™ technology, which is used for clinical treatment. Transducer arrays were placed with their centers and longitudinal axes in the xy-plane. A pair of arrays was systematically rotated around the z-axis of the head model, i.e. in the xy-plane, from 0 to 180 degrees, thereby covering the entire circumference of the head (by symmetry). The rotation interval was 15 degrees,



**Fig 1. Visualization of coordinate system, tumor locations and electrode rotation.** A. Axial section in the xy-plane of the GM and WM surface of the head model with all tumor locations superimposed (radiological orientation). X- and y-axes are shown to illustrate tumor center coordinates in millimeters. The tumor position  $x = 40$  mm,  $y = 0$  mm, and  $z = 0$  mm is indicated by a solid arrow. All tumors were located in the electrode plane, i.e.  $z = 0$  mm and had the following x- and y-coordinates: X-translations (mm): (30, 0, 0), (32.5, 0, 0), (35, 0, 0), (37.5, 0, 0), (40, 0, 0), (42.5, 0, 0), (45, 0, 0), (47.5, 0, 0), (50, 0, 0). Y-translations (mm): (40, -40, 0), (40, -30, 0), (40, -25, 0), (40, -20, 0), (40, -10, 0), (40, 0, 0), (40, 10, 0), (40, 15, 0), (40, 20, 0), (40, 25, 0), (40, 30, 0). B. Same section as shown in panel A, but with illustrations of the tested electrode rotations in the xy-plane from 0 to 180 degrees at 15-degree intervals. C. Surface view of the head model with one electrode array pair in the AP position, i.e. 0 degrees. The x-, y-, and z- axes are shown along with a schematic illustration of the rotations path of the electrode arrays on the skin.

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corresponding to approximately 2 cm translations, giving a total of twelve different positions in the range of 180 degrees (Fig 1C). Calculations were performed for electrode positions at all tumor locations.

Isotropic conductivity estimates corresponded to previous *in vivo* measurements at comparable frequencies [47±49]. Anisotropic conductivity tensor estimates were obtained for GM and WM using diffusion MRI and a linear direct mapping technique [50]. This mapping linearly rescales the diffusion tensors by a common factor to obtain the conductivity tensors. The scaling factor is chosen so that the geometric mean of the eigenvalues of the conductivity tensors fits as well as possible in a least-squares sense to isotropic reference values (0.276 S/m for GM, and 0.126 S/m for WM). For the remaining tissue types, the following isotropic conductivities were used: Tumor 0.24 S/m, necrosis 1.00 S/m, skin 0.25 S/m; bone 0.010 S/m; and CSF 1.654 S/m. These values are based on average values obtained from *in vitro* and *in vivo* experiments at comparable frequencies [51±54]. Additional detailed information about the methods used in this study can be found in Korshoej *et al.*, 2016 [35], and 2017 [36].

## Results

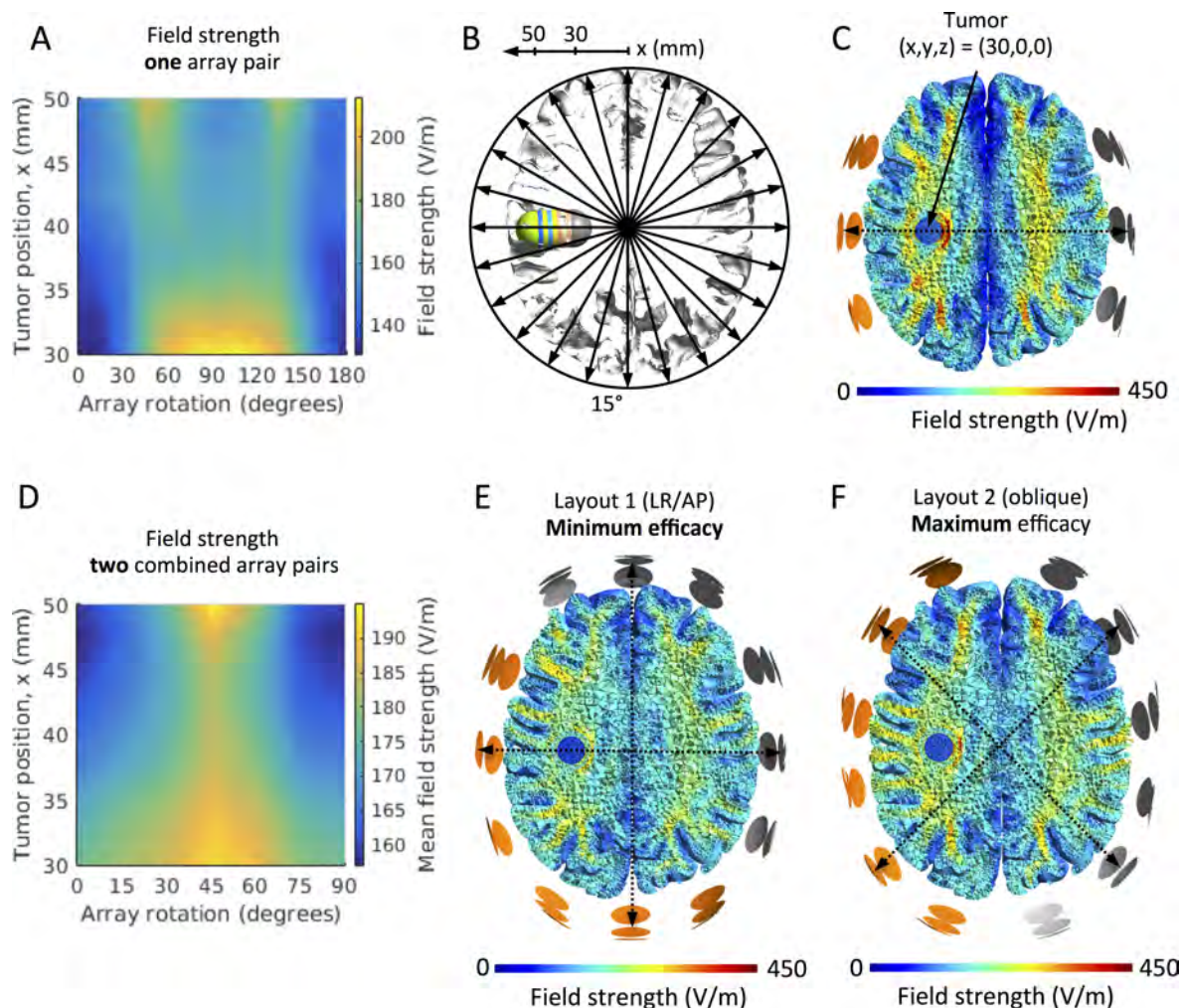
### Effect of array rotation

We investigated the impact of array rotation separately for tumors whose positions were varied along the x- and y-axes, respectively. Two-dimensional color maps were created to visualize the effect of rotation for different tumor positions systematically along each of the two axes. As previously described, TTFields therapy in its current form (Optune™) is applied using two sequentially active array pairs oriented orthogonally to each other. This is done to distribute the effect across cells dividing in different directions because the effect is higher when the field is applied in the direction of cell division [23]. To assess clinically relevant layout configurations, we, therefore, combined the results of all sets of array pairs oriented orthogonally to each other by calculating the average field induced by the two orthogonal pairs in the tumor tissue. This is equivalent to calculating the average peak field in the tumor over one duty cycle of TTFields for the given configuration and allows for direct efficacy assessment of orthogonal array configurations at different rotations around the head. The results are presented as both color maps as well as visual field maps showing the strength of the induced field in representative sections of the head model.

### Tumors translated in the left-right direction (x-axis)

The median field intensity in the tumor varied considerably with tumor location and array position (Fig 2). For all tumor locations, the direct AP array position at  $\theta = 0$  and 180 degrees induced the lowest median field strength ( $E = 131$  to  $148$  V/m). For tumors located in the cortical region, i.e. superficial to the sulcal fundi at  $x = 37.5$  to  $50$  mm, the field intensity showed two maxima at the oblique orientations of  $\theta = 45$  degrees ( $E = 165 \pm 193$  V/m) and  $\theta = 135$  degrees ( $E = 172 \pm 195$  V/m), respectively. This phenomenon is illustrated in Fig 2A. The field was slightly lower ( $E = 155 \pm 170$  V/m) for the LR array orientation,  $\theta = 90$  degrees. For tumors in the deeper subcortical regions ( $x = 30$  to  $35$  mm), the field showed a smooth curve with a single maximum at  $\theta = 90$  degrees ( $E = 179 \pm 209$  V/m). The field intensity at  $\theta = 90$  degrees increased for deeper tumor positions. Array positions at  $\theta = 45$  to  $\theta = 135$  degrees also induced high mean field intensities comparable to  $\theta = 90$  degrees. Fig 2C shows an example of the field distribution for the subcortical position  $x = 30$  mm. The supplementary material S1±S3 Videos show additional animations of the changing field distributions for all array rotations at representative tumor locations encompassing both cortical and subcortical positions, i.e.  $x = 30$  mm,  $x = 42.5$  mm, and  $x = 50$  mm, respectively.





**Fig 2. Effect of array rotation on field intensity for left-right tumor translations on the x-axis.** A. Color map of the median field intensity (V/m) in the tumors at varying x-positions (30 mm to 50 mm, *ordinate*) and varying rotations ( $\theta = 0$  to 180 degrees, *abscissa*) of a single pair of electrode arrays. Y- and z-coordinates were kept constantly at zero for all tumors, i.e. all tumors were in the center-to-center plane of the rotated array pairs. The figure shows field maxima at  $\theta = 45$  and 135 degrees, respectively, for all tumors between  $x = 35$  mm and 50 mm, while deeper seated tumors experienced high fields for all rotations between these values. B. Axial section of the GM and WM surfaces and the investigated tumors (x translations, i.e.  $x = 30$  to 50 mm,  $y = 0$  mm, and  $z = 0$  mm). Array rotations and tumor locations are indicated by the corresponding arrows and axis, respectively. C. Axial section (radiological convention) of the WM, GM and tumor volume ( $x = 30$  mm, position indicated by the solid arrow), showing an example of the topographical distribution of the field induced by TTFields (left-right array position,  $\theta = 90$  degrees). D. Color map comparable to panel A, but illustrating the mean field induced by two orthogonal array pairs. Tumor positions are indicated on the *ordinate* and the rotations of the posterior array on the *abscissa* ( $\theta = 0$  to 90 degrees). The figure shows a maximum mean field intensity at  $\theta = 45$  degrees equivalent to an oblique position of both pairs. The field distribution of this "optimal" layout is shown in panel F for the tumor position  $x = 30$  mm, while the distribution of the least effective layout ( $\theta = 0$  degrees) for the same tumor is shown in panel E.

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The average field strength induced by two orthogonal pairs of arrays was maximal at  $\theta = 45$  degrees, i.e. the combination of two oblique array pairs was superior to all other orthogonal combinations regardless of the tumor location along the x-axis (Fig 2D). In addition, S4 Video shows an animation of the sequence of field distributions induced by the optimal combination of orthogonal array pairs as the tumor is gradually translated from medial to lateral. As it is evident, the optimal array position is the oblique layout ( $\theta = 45$  degrees and  $\theta = 135$  degrees) for all tumors along the x-axis. The average field for the oblique layout was between  $E = 183$  V/m



and  $E = 195$  V/m depending on tumor position, and this corresponds to  $9 \pm 23\%$  enhancement compared to the least effective standard AP/LR layout at  $\theta = 0$  and  $90$  degrees. [Fig 2E and 2F](#) shows the topographical distribution of the average field for both the most effective array position  $\theta = 45/135$  degrees and the least effective  $\theta = 0/90$  degrees, respectively, at the tumor position ( $x = 30$  mm). Animations of the average field distributions for *combined* orthogonal arrays pairs are shown in the supplementary material [S4±S6 Videos](#) for all rotations and the same representative tumor locations,  $x = 30$  mm,  $x = 42.5$  mm and  $x = 50$  mm, as shown in [S1±S3 Videos](#).

### Tumors translated in the anterior-posterior direction, y-axis

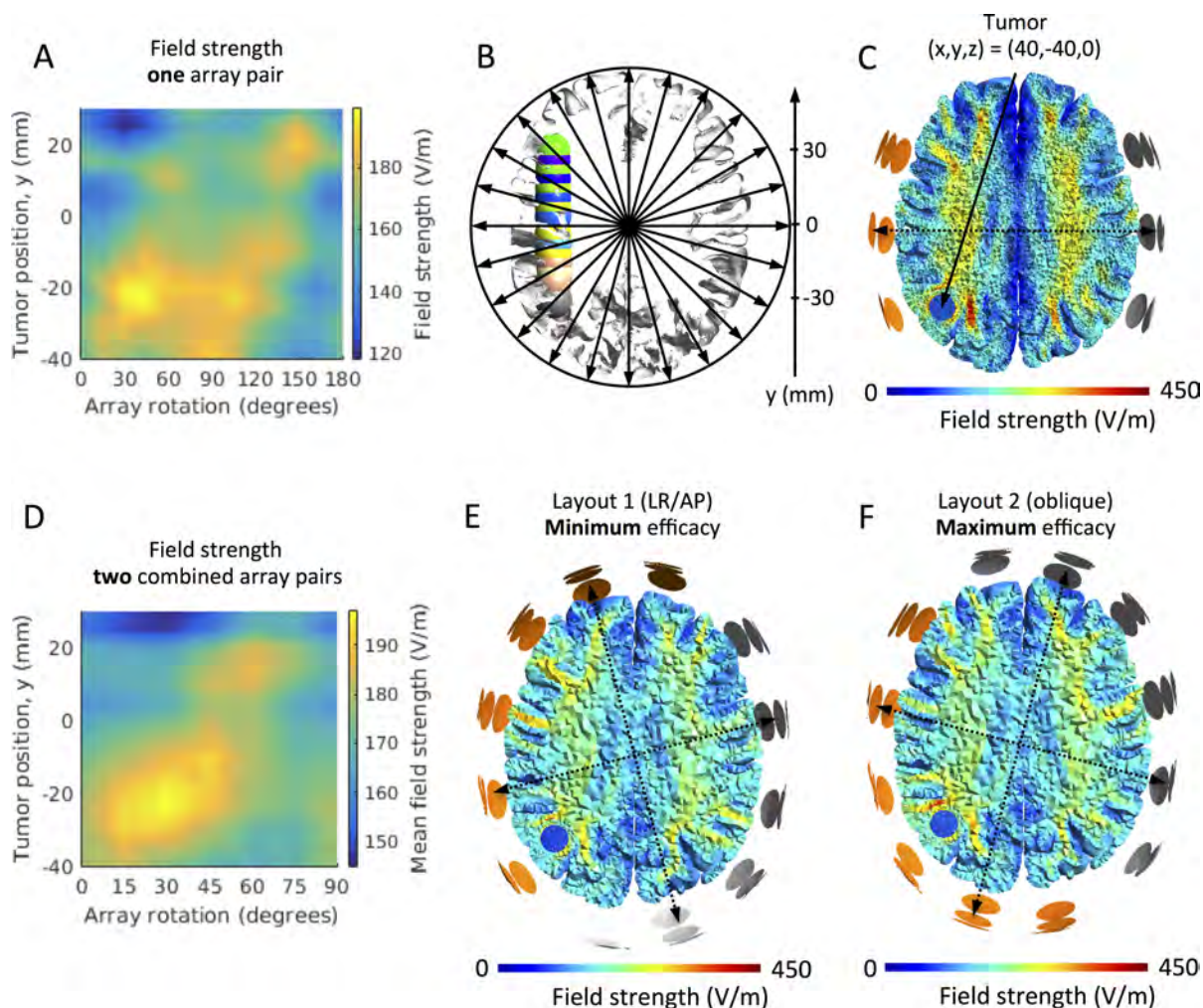
For most parietal and occipital tumors, i.e.  $y \leq 0$  mm, array positions between  $\theta = 15$  and  $\theta = 135$  degrees all tended to perform well and induced relatively high field values ([Fig 3](#)). For frontal tumors (i.e.  $y > 0$  mm) there was a tendency towards higher field values for array positions at  $\theta = 60$  degrees and higher. However, looking more closely at [Fig 3](#), we see that for most tumor positions in the anterior-posterior direction, there are two peaks in the plot of median field strength against different array rotations ([Fig 3A](#)), as it was also observed for cortical tumors translated in the left-right direction (see above). Correspondingly, the peak values also occurred at approximately orthogonal array positions. However, the array positions inducing peak field values varied with tumor location, as demonstrated in the oblique tendency of peak median field values in the color map. This observation is further illustrated in [Fig 3D](#), which shows the average median field strength for all combinations of two orthogonal pairs of electrode arrays. The figure shows, that *for every tumor position, an optimum position for each pair of orthogonal arrays exists. Furthermore, the optimum position is gradually rotated as the tumor is moved in the anterior-posterior direction.* This concept is further animated in the supplementary material [S8 Video](#), which shows the induced field distribution by the optimal array position for all tumors along the y-axis. As a general observation, for all the tumors the optimal layout was angled at approximately  $45$  degrees to the surface of the cortical region immediate overlying the tumor. Correspondingly, they were also oriented at approximately  $45$  degrees to the sulcal/gyral border in the vicinity of the tumor, as these were close to perpendicular to the brain surface. The field intensities induced by the optimum array layouts were generally  $10\%$  to  $17\%$  higher relative to the layout with the lowest efficacy. The oblique layout at  $\theta = 45$  degrees performed well for most tumor locations and better than the AP/LR layout ( $\theta = 0$  and  $90$  degrees) for all cases.

[Fig 3C](#) shows an example of the field distribution at the single array position ( $\theta = 90$  degrees) which induced maximum field intensity for a selected tumor at  $y = -40$  mm. Correspondingly, [Fig 3E and 3F](#) show examples of the orthogonal combination of electrode layouts with the highest ( $E = 183$  V/m) and lowest mean field intensity ( $E = 167$  V/m) for the same tumor location, respectively. The supplementary material [S9±S12 Videos](#), shows animations of the field distributions induced by single rotating array pairs for tumor locations spanning a large ( $7$  cm) anterior-posterior range, i.e.  $y = -40$  mm,  $y = -40$  mm,  $y = -20$  mm,  $y = 20$  mm, and  $y = 30$  mm. The corresponding distributions of *combined* orthogonal arrays pairs (mean field intensity) are shown in [S13±S16 Videos](#) for the same tumor positions, respectively.

### Discussion

In this study, we used realistic head models and finite element calculations to compute the distribution of TTFields for a large number of transducer array layouts and tumor positions. Specifically, we have investigated the impact of systematic rotation of a pair of transducer arrays around a central craniocaudal axis of the head on the dose of TTFields in nineteen





**Fig 3. Effect of array rotation on field intensity for anterior-posterior tumor translations, y-axis.** A. Color map of the median field intensity (V/m) in tumors at varying  $y$ -positions (-40 mm to 30 mm, *ordinate*) and varying rotations ( $\theta = 0$  to 180 degrees, *abscissa*) of a single pair of electrode arrays. X- and z-coordinates were kept constant at  $x = 40$  mm and  $z = 0$  mm, respectively, for all tumors, i.e. all tumors were in the center-to-center plane of the rotated array pairs. The figure shows field maxima at two separate rotations for the most tumors. The two maxima were separated by approximately 90 degrees. B. Axial section of the GM and WM surfaces and the investigated tumors ( $y$  translations, i.e.  $x = 40$  mm,  $y = -40$  to 30 mm, and  $z = 0$  mm). Array rotations and tumor locations are indicated by the corresponding arrows and the axis, respectively. C. Axial section (radiological convention) of the WM, GM and tumor volume ( $y = -40$  mm, position indicated with a solid arrow), showing an example of the topographical distribution of the field induced by TTFields (left-right array position,  $\theta = 90$  degrees). D. Color map comparable to panel A, but illustrating the mean field induced by two orthogonal array pairs. Tumor positions are indicated on the *ordinate* and the rotations of the posterior array on the *abscissa* ( $\theta = 0$  to 90 degrees). The figure shows a single maximum of the mean field intensity at varying rotations depending on the tumor of interest. The field distribution of the "optimal" layout is shown in panel F for the tumor position  $y = -40$  mm, while the distribution of the least effective layout ( $\theta = 0$  degrees) for the same tumor is shown in panel E.

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systematically varied tumor positions. We have identified optimum array positions for each tumor position and presented elaborate animations and graphical representations to provide users with a more intuitive understanding of the effect and distribution of TTFields and how this depends on the tumor and electrode array position.

As general observations, we found that varying the array layout produced markedly different field distributions and that the array position had a great impact (up to 23%) on the median field intensity observed in the tumor region for all studied tumor positions. In particular,



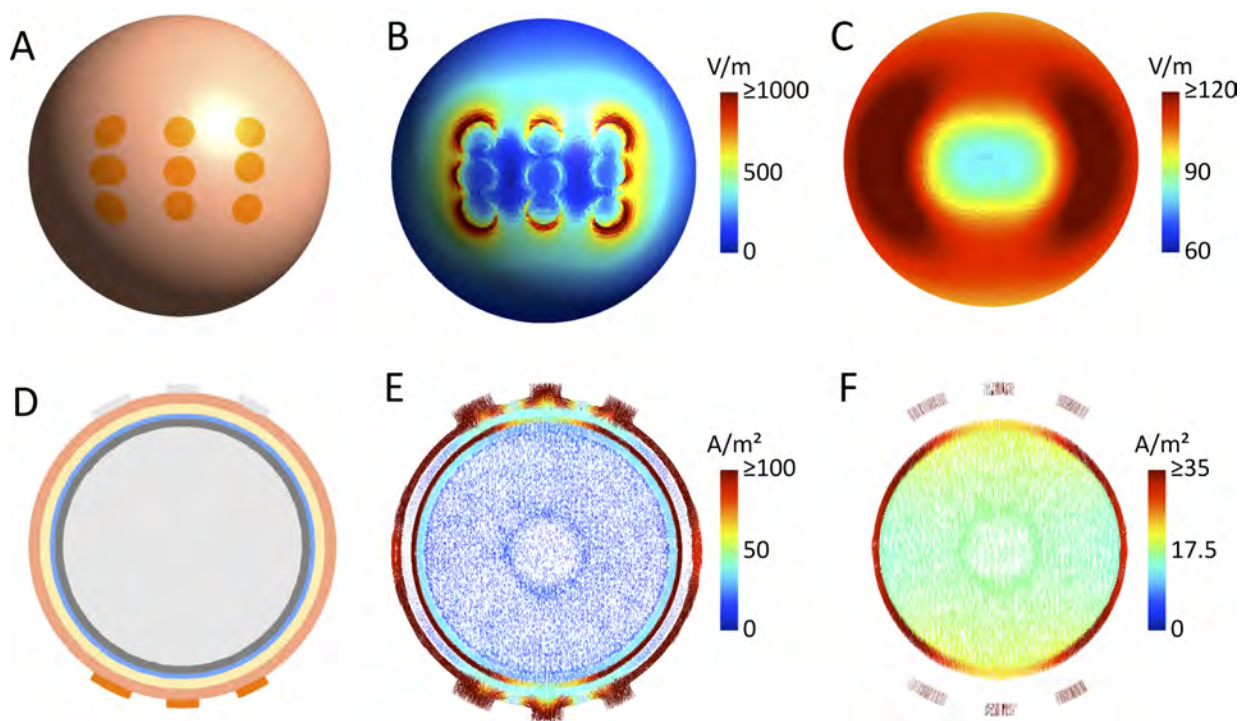
when varying the tumor from left to right (Fig 2A), there was a bimodal dependency between the field intensity in the tumor and the array position, meaning that the field dose peaked at two separate (optimal) array positions. This result was observed for most superficial tumor positions in the cortical regions. In addition, the two optimal array positions were close to orthogonal for most tumors, i.e. positioned at ninety-degree intervals to each other. In the deeper subcortical regions, we observed a single optimum array position at which the field was maximal ( $\theta = 90$  degrees), however, high field intensities were observed for a wide range (45 to 135 degrees) of electrode positions, and the optimum combination of two orthogonal field pairs had a single peak at  $\theta = 45$  degrees as observed for the superficial tumors on the x-axis.

When varying the tumor position in the anterior-posterior direction, we observed a significant dependency between the optimum array configuration and the tumor position. Specifically, the optimum position of the orthogonal pair of arrays was gradually shifted clock-wise as the tumor was moved from posterior to anterior positions (viewed in radiological convention). However, array positions between  $\theta = 15$  and 135 degrees were all relatively effective for most parietooccipital tumors, while rotations of  $\theta = 135$  degrees or higher were generally more effective for frontal tumor locations.

Due to the size of the electrode arrays, superficial tumors in our simulations were close to one of the outer electrode columns of an array for the oblique array orientations. It is interesting to note that the fields in the more superficial brain regions tend to be stronger underneath the outer electrodes than the central electrode of an array (see, e.g. S3 Video). This resembles the well-known edge effect for large pad electrodes used in transcranial electric brain stimulation [55], due to which the field is higher underneath the edges compared to the center of these electrode pads. Here, given that all electrodes of a TTFields electrode array are connected to the same channel and thus have the same electric potential, the same effect occurs and causes an unequal distribution of the current strength across the electrodes, with the outer electrodes tending to induce stronger currents into the underlying skin area (Fig 4 shows this exemplarily for a spherical head model). This effect is influenced by the local tissue conductivities underneath the electrodes (e.g., thin vs. thick skull) and thus varies across array orientations. However, the simulation results indicate that it is observed for the majority of orientations. As a consequence, when employing orthogonal pairs of arrays at an oblique orientation, superficial tumors will be close to an outer electrode column of one of the arrays for each of the two pairs, resulting in high median field strength. This explains the superiority of the 45° layout compared to the standard LR and AP electrode montages for the superficial tumor positions when varying the position from left to right. This effect is further increased by the generally low field intensity caused by the AP electrode array pair (0 and 180 degrees in Fig 2A; please refer to Korshoej *et al.* (2017) for a discussion of the reasons underlying the differences between LR and AP). The enhanced field intensities underneath the outer electrode columns also explain the gradual shift of the optimal array orientation when varying the tumor position from posterior to anterior. This is exemplified by the superficial tumor location  $x = 50$  mm ( $y = 0$  mm and  $z = 0$  mm), which experienced the strongest fields at 45 degrees and 135 degrees, when the tumor was closest to the anterior and posterior electrode columns, respectively, S3 Video. The reduction of field intensity at angles between the two maxima (minimum at the left/right array position, Fig 2A) may also be explained in part by the edge effect because lower currents are induced underneath the central electrode. A likely contributing factor, however, is the fact that increasing amounts of current are shunted through the sulci and thus pass the tumor when the field is oriented increasingly in parallel with the sulci, i.e. close to the LR position.

The LR and AP configuration is a commonly employed layout for a wide range of tumors *In this study, we find that the vast majority of the investigated cases would benefit more from the oblique configuration (45 degrees to the sagittal plane) than from the LR/AP array configuration,*





**Fig 4. "Edge" effects for 3x3 electrode arrays.** A. One of the two electrode arrays seen from above. B. Electric field distribution on the skin surface. The higher field strengths at the outer edges of the electrode array are clearly visible. C. Electric field distribution on the GM surface. The distribution is smoother than on the skin surface, but the lower field strengths underneath the array center are still clearly observed. D. Cut through the spherical head model. It consists of a central WM sphere ( $r = 7.5$  cm), surrounded by GM (outer  $r = 8.0$  cm), CSF (outer  $r = 8.3$  cm), skull (outer  $r = 8.9$  cm) and skin (outer  $r = 9.5$  cm). The same tissue conductivities as for the head model were used, see [Methods](#). GM and WM were modelled as isotropic with  $\sigma_{GM} = 0.276$  S/m and  $\sigma_{WM} = 0.126$  S/m. E. Current flow in the plane shown in D. The lower current densities in the skin and CSF layers underneath the central electrode are clearly observable (the different arrow densities in the sphere center are an artefact of the meshing process and do not influence the results). F. Current flow in GM and WM in the same plane. The lower current densities in the GM layer underneath the central electrode are clearly visible.

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although even further optimization may be performed in accordance with the above results. Specifically, the field was maximized when the neighboring arrays were orthogonal and placed such that their outermost columns of electrodes were close to the tumor. We found that each tumor position was associated with a single optimum position of two orthogonal array pairs, at which the induced field was highest. From a treatment efficacy point of view, the ninety-degree relationship between optimal array positions (bimodality, Figs 2A and 3A) is highly convenient. This is because clinical TTFields therapy is performed with two orthogonal pairs of arrays in order to target cells with a different (random) direction of mitosis and distribute the tumor-inhibiting effect across larger regions of the pathology [23].

In general, our observations support the notion that the dose of TTFields, and therefore expectedly also the therapeutic efficacy, depends significantly on the positioning of transducer arrays on the scalp. Under normal circumstances, a personalized layout is produced for each patient prior to treatment initiation, using the software NovoTAL™ (Novocure, Ltd.). Very often, however, clinicians are faced with the challenge of having to deviate from the optimum layout due to various circumstances, such as scar tissue, use of metallic bone-fixation implants following surgery, or shunt therapy, etc. In addition, patients are recommended to move the arrays by approximately 2 cm when they are changed every  $3 \pm 4$  days. This is done to minimize the risk of skin rash beneath the electrodes, which is a commonly observed side effect of TTFields therapy. Our results may be used to support clinicians and users in deciding optimal



array layouts for patients undergoing therapy, when facing challenges as described above. Of the tumors investigated, many would be treated with the LR and AP array layouts. This layout is produced from FE calculations of the field distribution, based on field head models adapted to the individual head and tumor morphometrics comparable to the approach used here. Our results suggest that some patients may in fact benefit more from the oblique array layout or layouts adapted in accordance with the above. In any case, the results presented provide viable alternative layouts for a wide range of tumors.

## Limitations and future perspectives

It is important to highlight that the investigated model reflects a limited, but comprehensive variety of scenarios specific for the individual case. Although a large number of tumor and array positions were investigated, personalized modeling experiments should ideally be conducted to account for the complex individual variations in anatomy and (as far as possible) tissue conductivities, including the shape and size of the head and tumor, observed in real tumor patients. Personalized approaches may account more accurately for the expected treatment efficacy and support more precise, safe and efficacious treatment planning. In addition, personalized approaches based on new and representative MRI data would enable a better and timelier characterization of the TTFields distribution at the moment of interest. Thereby the model would better account for changes, e.g. in tumor size or tissue composition, which may occur during the course of TTFields treatment as a result of disease development or therapy. Recently, the authors published an example of an individualized approach to TTFields modeling.

It should also be emphasized that the ohmic conductivity estimates used in the model markedly influence the results of the field calculations (see [Methods](#)). Recent studies by Wenger *et al.*, 2015 [31], and Lok *et al.*, 2017 [33], assessed the sensitivity of TTFields FEM models, such as the one employed in this study, towards dielectric property variations. They conclude that the conductivity variations significantly influence the distribution of TTFields, while permittivity variations only play an insignificant role. In this study, we thus neglected the influence of permittivity and have employed common conductivity values taken from the literature. However, it should be emphasized that the biological tissue conductivities have not been firmly established at 200 kHz, so that the resulting uncertainty might impact the generalizability of our results. However, since the field changes observed with changing tumor and electrode position were primarily associated with relative differences in conductivity between brain tissue, tumor tissue, and CSF [36], the observations reported will likely hold for a range of conductivity variations, as long as the differences in conductivity are in the same direction, i.e. the conductivity of CSF is higher than the conductivity of tumor, and the conductivity of tumor is higher than the conductivity of brain tissue. Although the absolute field values will change with varying conductivities, we expect that our main findings and conclusions will hold for a wide range of scenarios.

In addition to field intensity, future models should ideally also incorporate information about exposure time and the amount of non-orthogonality (i.e., directional correlation) of the electric fields that are induced by the two electrode array pairs in the tumor. The latter aspect relates to the finding that the effects of TTFields on a dividing cancer cell are enhanced when the field is aligned with the direction of cell division. Given that this direction varies randomly across tumor cells, treatment efficacy seems to be improved when two or more oblique fields rather than a single field direction are used [23]. Also, future models should incorporate better segmentations of the pathology to obtain representative field estimates in the true regions of interest. Finally, it is important to highlight that future consideration should also be given to validating the simulation results by means of direct TTFields measurements in vivo.



## Conclusion

We present novel findings, describing the impact of systematic positional variation of TTFields electrode arrays on a human head for a large number of tumor locations in the brain. For most superficial tumor positions, we found that there were two optimal array positions, at which the median field intensity was highest. These varied systematically (i.e. clockwise rotation), as the tumor position was translated from posterior to anterior, while it was unaffected by left-right tumor translations. In addition, the two optimal layouts were oriented approximately orthogonally to each other. Correspondingly, we found that there was a single optimal layout of combined orthogonal array pairs, at which the median TTFields dose was highest. The optimum position also varied systematically in accordance with the above and in general, the optimum arrays were oriented at 45 degrees to the surface of the brain immediately overlying the tumor. We also found that one particular layout was more effective for most tumor locations compared to the standard LR and AP combination of array pairs. This layout was composed of two orthogonal and oblique array positions both oriented at 45 degrees to the mid-sagittal plane. The presented results may generally guide layout configuration in clinical cases where deviations from the suggested NovoTAL layout are required, e.g. due to therapy-induced skin rash, etc. Furthermore, the oblique configuration may potentially be used as an effective, alternative layout for most tumors although further optimization may be expected by direct comparison with tumor representative locations. In addition, our results present extensive animations and graphical representations, to illustrate the impact of tumor and electrode positions on the distribution of TTFields. Our results will hopefully improve users' understanding of TTFields and support clinical decisions on TTFields therapy.

The modeling approach used in this study is widely adopted. However, it must be noted that variations in tissue conductivities and head morphology are likely to affect the results. Further studies are required to estimate the robustness and sensitivity of the suggested conclusions towards these variations. Also, accurate field estimation should ideally be computed from patient-specific head models, which accurately represent the anatomy and tissue conductivity of the given individual.

## Supporting information

**S1 Video.** Field distribution for rotation of a single array pair at the tumor position  $x = 30$  mm.

(MP4)

**S2 Video.** Field distribution for rotation of a single array pair at the tumor position  $x = 42.5$  mm.

(MP4)

**S3 Video.** Field distribution for rotation of a single array pair at the tumor position  $x = 50$  mm.

(MP4)

**S4 Video.** Field distribution of optimal array position for all tumors translated in the left-right direction.

(MP4)

**S5 Video.** Field distribution for orthogonal array pairs at various rotations and tumor position  $x = 30$  mm.

(MP4)



**S6 Video.** Field distribution for orthogonal array pairs at various rotations and tumor position  $x = 42.5$  mm.

(MP4)

**S7 Video.** Field distribution for orthogonal array pairs at various rotations and tumor position  $x = 50$  mm.

(MP4)

**S8 Video.** Field distribution of optimal array position for all tumors in the anterior-posterior direction.

(MP4)

**S9 Video.** Field distribution for rotation of a single array pair at the tumor position  $y = -40$  mm.

(MP4)

**S10 Video.** Field distribution for rotation of a single array pair at the tumor position  $y = -20$  mm.

(MP4)

**S11 Video.** Field distribution for rotation of a single array pair at the tumor position  $y = 20$  mm.

(MP4)

**S12 Video.** Field distribution for rotation of a single array pair at the tumor position  $y = 30$  mm.

(MP4)

**S13 Video.** Field distribution for orthogonal array pairs at various rotations and tumor position  $y = -40$  mm.

(MP4)

**S14 Video.** Field distribution for orthogonal array pairs at various rotations and tumor position  $y = -20$  mm.

(MP4)

**S15 Video.** Field distribution for orthogonal array pairs at various rotations and tumor position  $y = 20$  mm.

(MP4)

**S16 Video.** Field distribution for orthogonal array pairs at various rotations and tumor position  $y = 30$  mm.

(MP4)

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Regarding the randomization, women were randomized by a web-based system (<http://www.randomization.com>) using random blocks of 2, 4, and 6 to receive the pessary or no pessary. Randomization was stratified by cervical length, and separate randomization sequences were created by an independent statistician. However, there was an error in the article. The randomization strata were less than 20 mm and equal or greater than 20 mm to equal or less than 25 mm, not equal or less than 20 mm and greater than 20 mm to equal or less than 25 mm as stated. Using the erroneous cutoff would lead to imbalance between the groups, as Thornton suggested. However, with the correct cutoff, no imbalance was noticed, with 125 women with a cervical length less than 20 mm and 25 women with a cervical length equal or greater than 20 mm to equal or less than 25 mm in each group. The number of women with a cervical length equal or less than 20 mm in Table 1 was correct, as equal or less than 20 mm was the cutoff used for vaginal progesterone therapy, as recommended by guidelines.<sup>2</sup> The article has been corrected online and we apologize for any confusion this may have caused.

Regarding the Kaplan-Meier curves, the numbers of women at risk, reported in Figure 2, were the total number of randomized women minus the number of women who already delivered, regardless of whether they had iatrogenic or spontaneous preterm birth. Therefore, the numbers of women at risk are the same for both curves.

The benefits of the pessary shown in our trial could be explained by the high treatment adherence compared with other trials. There are several ongoing trials evaluating the efficacy of cervical pessary in prevention of preterm birth, and there are plans for an individual patient data meta-analysis that will include our data. The meta-analysis will update prior reviews<sup>3,4</sup> and hopefully will clarify the effect of cervical pessary in prevention of preterm birth.

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**Conflict of Interest Disclosures:** Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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## Quality of Life in Patients With Glioblastoma Treated With Tumor-Treating Fields

**To the Editor** In a multisite, randomized, phase 3, clinical trial, Dr Stupp and colleagues<sup>1</sup> demonstrated a modest benefit for patients newly diagnosed with glioblastoma treated with tumor-treating fields (TTFields) and temozolomide vs temozolomide alone in progression-free survival (7.1 months for TTFields plus temozolomide vs 4 months for temozolomide alone) and overall survival (20.9 months for TTFields plus temozolomide vs 16 months for temozolomide alone). The authors should justify the current cost of the device (\$20 000 per month) and also discuss the effect on quality of life for both the patients (shaving their head) and family when patients wear the TTFields device 18 hours a day.

Cognitive (Mini-Mental State Examination) and functional (Karnofsky performance score) metrics were included in their analysis, but the use of standardized, health-related quality-of-life scores (such as the European Organisation for Research and Treatment of Cancer quality-of-life questionnaire and its brain-specific module) were not mentioned. Tumor-treating fields plus temozolomide compared with temozolomide alone showed no significant differences in time to a sustained 6-point decline in the Mini-Mental State Examination score.<sup>1</sup> Standardized health-related quality-of-life scores take into account emotional, social, and role functioning.<sup>2</sup> An interim analysis conducted on the first 315 randomized patients did not show significant differences for any of the functional scales on either questionnaire in either treatment group.<sup>2</sup> A larger analysis incorporating 92% of the patients noted that 42% of patients had not completed the questionnaires at the 1-year follow-up.<sup>3</sup> The physical and emotional burden of shaving one's head while wearing the device 18 hours a day (including while sleeping) cannot be underestimated for both patient and family members. In fact, it is the partner, friend, or family member who must change the adhesives, administer scalp care, and adjust the TTFields device when it malfunctions, even in the middle of the night.

Other trials, perhaps with less significant psychiatric implications, may be better suited for patients with newly diagnosed glioblastoma. For example, a phase 3 trial (CeTeg/NOA-09) showed that the combination of lomustine and temozolomide significantly improved median overall survival (37.9 months with lomustine, temozolomide, and radiotherapy vs 31.4 months with temozolomide and radiotherapy alone) in patients with the O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT) promoter.<sup>4</sup>

In sum, although TTFields plus temozolomide provides an interesting and innovative treatment for newly diagnosed glioblastoma, a better understanding of the effect on patient and family quality of life needs to be assessed, especially to justify TTFields's increased economic and emotional burden.

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**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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**In Reply** Our randomized trial demonstrated a consistent improvement in both progression-free and overall survival when TTFields was included in first-line therapy for glioblastoma. The hazard ratio for death was 0.63, translating into an improvement in the 2-year survival rate from 31% to 43%. For comparison, the addition of temozolomide to radiotherapy compared with radiotherapy alone also resulted in a hazard ratio of 0.63, with a 2-year survival rate increasing from 10% to 27%.<sup>1</sup> One may consider the improvements modest, yet these are the most effective proven treatments available.

Cancer treatments, be it surgery, irradiation, chemotherapy, or TTFields, all have their inherent toxicities and inconveniences. The results of the health-related quality-of-life analyses that Dr Kwan and colleagues requested have recently been published in detail.<sup>2</sup> The main adverse effect of TTFields was skin reactions (mostly mild) at the site of electrode placement. We hypothesized that wearing the device could either decrease health-related quality of life through its burden on the patient, including physical impairment or a decreased social or role functioning due to the visibility of the device, or increase it through an improved feeling of well-being related to active participation of both the patient and the caregiver in the fight against the disease. Instead, no statistically significant differences in health-related quality of life between baseline and 12 months were observed between groups, except for itchy skin in the TTFields group. Health-related quality-of-life scores were maintained for a longer period in the TTFields group due to the longer time to tumor progression and survival. Missing longitudinal quality-of-life data are an inherent problem of many studies as is overrepresentation of patients with favorable prognostic factors. However, our mixed-model analyses, accounting for missing data, confirmed the results found in the mean change from baseline analyses.

Kwan and colleagues point out that there may be other treatments that could confer a benefit in outcome. We embrace any future advances made in the treatment of patients with malignant glioma. The TTFields treatment has no overlapping toxicities and thus could be combined with any other

promising therapy; TTFields treatment is an important step toward improvement in survival, but further research is needed to ultimately cure patients with glioblastoma.

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**Conflict of Interest Disclosures:** Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Stupp reported fees paid to his institution from and serving on advisory boards of Celgene, Novartis, AbbVie, and Merck KGaA (Darmstadt) and travel support from Novocure and that his spouse works full time for Novartis. Dr Ram reported that he has received grants, personal fees, stock, and nonfinancial support from Novocure.

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## The National Resident Matching Program and Competition for Employment

**To the Editor** Dr Curtin and Ms Signer<sup>1</sup> advocated for the policies of the National Resident Matching Program (NRMP) to maintain “a fair, efficient, and reliable matching process.” However, we believe this article minimizes the inherent inequity of the NRMP binding match commitment, which requires medical students to enter the Match contractually obligated to an employment agreement they have never seen. Matched applicants are then not allowed any negotiation of the employment agreement that they were bound to sign. Rigorous enforcement of these contracts are justified by Curtin and Signer to ensure the “integrity” of the process, which is the only means of securing residency positions in the United States.

The contractual obligation of resident physicians to the NRMP fundamentally violates antitrust laws by undermining competition in recruitment and hiring, thereby lessening employment choice and compensation. In the face of a court challenge to the NRMP, the process has been protected from legal scrutiny by Congress. This was accomplished through an exemption of the NRMP in an amendment to the unrelated Pension Fund Equity Act of 2004. The amendment, which had not undergone hearings before appropriate committees, retroactively and permanently exempted graduate medical education programs from antitrust law.

We agree that the NRMP is efficient and effective; in fact, the 2012 Nobel Prize in Economics was awarded for the algorithm on which the NRMP is based.<sup>2</sup> However, the Congressional exemption of the NRMP from antitrust laws and the secretive means by which it was enacted were not proper. The amendment to the Pension Fund Equity Act of 2004 was not procompetitive, as it prevents fair negotiations at the heart of all employment agreements.<sup>3</sup>





# Dosimetric Impact of a Tumor Treating Fields Device for Glioblastoma Patients Undergoing Simultaneous Radiation Therapy

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**Purpose:** A recent randomized phase III clinical trial in patients with glioblastoma demonstrated the efficacy of tumor treating fields (TTFields), in which alternating electric fields are applied via transducer arrays to a patient's scalp. This treatment, when added to standard of care therapy, was shown to increase overall survival from 16 to 20.9 months. These results have generated significant interest in incorporating the use of TTFields during postoperative concurrent chemoradiation. However, the dosimetric impact of high-density electrodes on the scalp, within the radiation field, is unknown.

**Methods:** The dosimetric impact of TTFields electrodes in the radiation field was quantified in two ways: (1) dose calculated in a treatment planning system and (2) physical measurements of surface and deep doses. In the dose calculation comparison, a volumetric-modulated-arc-therapy (VMAT) radiation plan was developed on a CT scan without electrodes and then recalculated with electrodes. For physical measurements, the surface dose underneath TTFields electrodes were measured using a parallel plate ionization chamber and compared to measurements without electrodes for various incident beam angles and for 12 VMAT arc deliveries. Deep dose measurements were conducted for five VMAT plans using Scandidos Delta4 diode array: measured doses on two orthogonal diode arrays were compared.

**Results:** In the treatment planning system, the presence of the TTFields device caused mean reduction of PTV dose of 0.5–1%, and a mean increase in scalp dose of 0.5–1 Gy. Physical measurement showed increases of surface dose directly underneath by 30–110% for open fields with varying beam angles and by 70–160% for VMAT deliveries. Deep dose measurement by diode array showed dose decrease of 1–2% in most areas shadowed by the electrodes (max decrease 2.54%).

**Conclusion:** The skin dose in patients being treated with cranial irradiation for glioblastoma may increase substantially (130–260%) with the addition of concurrent TTFields electrodes on the scalp. However, the impact of dose attenuation by the electrodes on deep dose during VMAT treatment is of much smaller, but measurable, magnitude (1–2%). Clinical trials exploring concurrent TTFields with cranial irradiation for glioblastoma may utilize scalp-sparing techniques to mitigate any potential increase in skin toxicity.

**Keywords:** glioblastoma multiforme, radiation therapy, tumor-treating fields, dose calculation, skin dose



## INTRODUCTION

Glioblastoma remains the most common primary brain malignancy, with more than 13,000 patients diagnosed in 2017 in the United States (1). The median overall survival for patients diagnosed with glioblastoma is dismal, ranging from 15 to 16 months in prospective randomized studies performed in the first decade of this century (2, 3). This median survival resulted from the introduction of temozolomide, an alkylating chemotherapy given concurrently and adjuvantly with radiation therapy (RT) after maximal safe neurosurgical resection; prior to the use of temozolomide, clinical trials routinely demonstrated a median survival of approximately 12 months. The poor prognosis of this disease has motivated clinical trials of radiation dose escalation, novel drug therapies, and other unconventional approaches. The most successful of these approaches has been the introduction of tumor treating fields (TTFields), in which alternating electric fields are applied *via* transducer arrays to a patient's scalp. This technique has been demonstrated to have anti-mitotic activity in tumor cells and showed promise in patients with recurrent disease (4–7). The technique was applied in patients immediately after the conclusion of adjuvant chemoradiation in a randomized phase III study, which showed increased overall survival from 16 to 20.9 months (8).

This remarkable improvement has generated significant interest in the use of TTFields earlier in the treatment course—that is, during the course of postoperative concurrent chemoradiation—in an attempt to evaluate the potential synergistic effect of multimodality therapy. However, the delivery of TTFields requires the placement of metallic transducer electrodes of high density onto the scalp of patients, directly into the radiation field. The dosimetric impact of an array of electrodes placed directly in the radiation field is not precisely known, and without this knowledge, estimation of the potential for toxicity with combined therapy is more difficult.

High-density objects on the surface of the patients receiving RT can have non-negligible and competing effects on the dose distribution in the patient's body. On the one hand, the metal acts like additional buildup material, generating additional electrons *via* the photoelectric effect or Compton process. Clinically, this could translate into increased skin dose below the TTFields electrodes.

On the other hand, high-density materials can also act as an attenuator, reducing the dose to deeper tissues while simultaneously hardening the radiation beam *via* preferential attenuation of low energy photons. Clinically, this may impact the percentage depth dose curve and potentially decrease the target volume dose.

The present work is thus motivated by these physical principles, as well as the improvement in clinical outcomes with TTFields. We investigate both the buildup and attenuation/filtering effects of the TTFields electrode array on a scalp phantom, using both advanced dose calculation algorithms in the treatment planning environment and physical measurements of electrodes impact on surface and deep dose. We hypothesize that quantification of the dosimetric impact of the electrodes may facilitate the development and execution of clinical trials evaluating combination

chemoradiation and TTFields for patients with newly diagnosed glioblastoma.

## MATERIALS AND METHODS

### Planning Study

The planning study was done on the Anderson RANDO phantom. A CT scan of the phantom was acquired, with and without the TTFields device. Target volumes and organs-at-risk contours from 10 patients previously treated for glioblastoma were used to generate clinical contours on the RANDO phantom. The target and normal tissues from these cases were transferred to the RANDO phantom and then modified by a radiation oncologist to be as realistic as possible.

These phantom patients were each planned using volumetric-modulated-arc-therapy (VMAT) in Varian Eclipse® treatment planning system. Planning techniques were duplicated from the original clinical treatment plans for the number of arcs and the arc angle ranges. The metal electrodes from the TTFields treatment devices were contoured on the CT scans and assigned a fixed density equal to the highest allowable value in each treatment planning system, which is around the density of aluminum, to reduce the impact from metal artifacts on dose calculation and maintain consistent electrode positions between different phantom plans. The dose calculation algorithm was set to AcurosXB v11 for its higher accuracy on calculating dose around high-Z materials (9).

All treatment plans were optimized on the scan without electrodes, which is how patients would be scanned and simulated during an actual clinical treatment plan design process. The prescription dose for all plans in this study was 60 in 2 Gy per fraction. Normal tissue objectives followed RTOG 0825 protocol: brainstem Dmax < 60 Gy, optical chiasm Dmax < 56 Gy, optical nerves Dmax < 55 Gy, lenses Dmax < 7 Gy, scalp Dmean < 20 Gy, scalp D20cc < 40 Gy, and scalp D10cc < 50 Gy. Plans were normalized so that the 100% prescription line covers 95% of the PTV volume. While keeping all plan parameters the same, the dose distribution was then recalculated on the phantom with the metal electrodes to assess the impact from the electrodes on key dosimetric parameters.

Paired comparison between treatment plans with and without electrodes were performed first for PTV coverage using percentage of PTV receiving at least Rx dose. The scalp dose was also compared to assess the dose buildup effect caused by the presence of metal object close to the skin. All comparisons were tested using Wilcoxon signed rank test to determine statistical significance.

### Physical Measurements

To further evaluate the impact of skin and deep doses from the presence of the TTFields electrodes, physical measurements were also conducted.

Surface dose changes were measured using a parallel plate ionization chamber (10). The chamber was placed in the solid water phantom with 10 cm backscatter, and the surface of the chamber was matched with the surface of the phantom. To protect the chamber, a 0.87 mm acrylic cap was placed on the front window of the parallel plate chamber, making the effective point of measurement at 1 mm depth in tissue equivalent media. The TTFields electrodes



were then placed on top of the acrylic cap to mimic placement on a patient's scalp. The radius of active volume of the chamber was much less than the radius of the electrodes; therefore, the partial volume effect as a result of the electrode partially blocking the chamber was minimized. All measurements were first performed with 10 cm × 10 cm field size at 100 cm SSD. Charges were collected with and without TTFields electrodes for incident beam angles at  $-85^\circ$ ,  $-75^\circ$ ,  $60^\circ$ ,  $30^\circ$ ,  $0^\circ$ ,  $30^\circ$ ,  $60^\circ$ ,  $75^\circ$ , and  $85^\circ$  relative to the axis perpendicular to the surface of the chamber. In addition, surface doses with and without TTFields electrodes were also compared using actual VMAT plans delivered to a 20 cm × 20 cm × 20 cm solid water phantom. Surface doses for VMAT plans were measured with

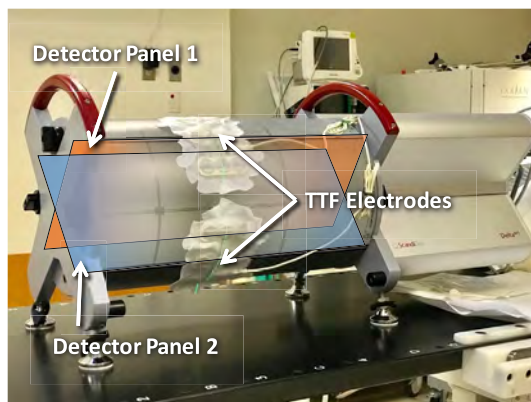
above-mentioned parallel plate chambers mounted with a special inset on the surface of the solid water phantom, with the chamber's measurement window flush to the solid water phantom surface to mimic the actual scatter condition from the patient. Other *in vivo* dosimetry devices such as thermal luminescence dosimeter (TLD) or optically stimulated luminescence dosimeter (OSLD) were not chosen because of unavailability (TLD) and larger measurement uncertainty ( $\sim 5\%$  for OSLD).

In addition to surface dose, deep dose measurements were conducted using Delta4 device (Scandidos AB, Sweden) that are currently used clinically to verify all VMAT treatment in our clinic (11). As shown in **Figure 1**, this device has two planes of diode arrays that measures dose distribution within a cylindrical phantom. To mimic clinical treatment with TTFields, the electrodes were placed directly onto the surface of the phantom where beams would enter. The measurements were compared with and without electrodes. Histograms and mean dose deviation were used to assess deep dose differences caused by the TTFields electrodes.

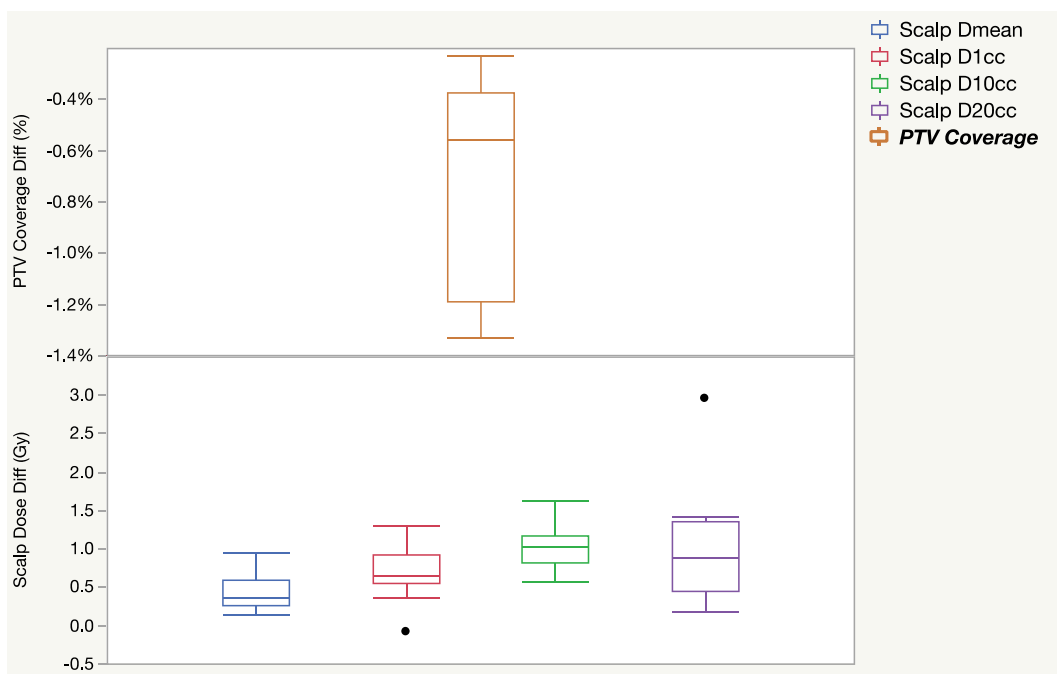
## RESULTS

### Plan Dosimetry Evaluation

**Figure 2** shows the difference in PTV coverage and scalp dose when comparing dose calculated with TTField electrodes in place against dose calculated without electrodes for 10 patients. In general, the calculated dose with the presence of electrodes decreased PTV coverage by  $0.7 \pm 0.4\%$  in the treatment planning system. Dose to the scalp were slightly elevated when electrodes were taken into consideration during dose calculation. Mean scalp dose, as measured by the D1cc, D10cc, and D20cc were on average 0.5–1 Gy higher. Wilcoxon signed rank tests for all

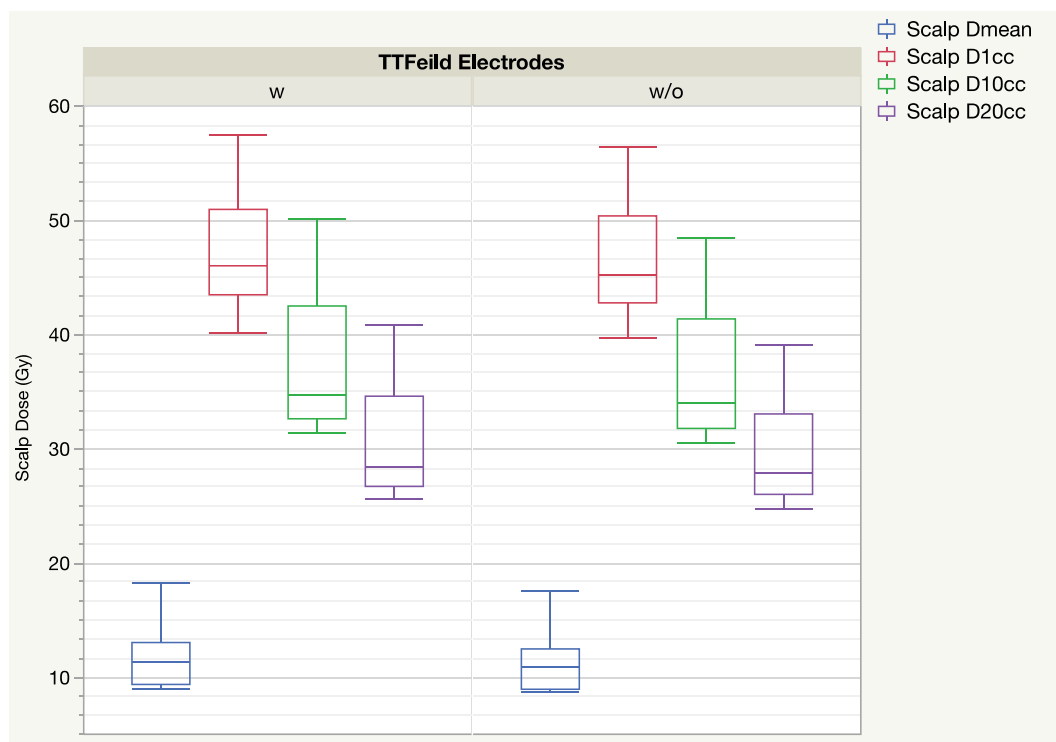


**FIGURE 1** | Measurements on deep dose impact from tumor treating fields (TTFields) electrodes conducted using the Delta4 volumetric-modulated-arc-therapy QA platform. Blue and amber overlays showing the position and directions of orthogonal detector panels 1 and 2.



**FIGURE 2** | Dosimetric differences in PTV coverage and scalp dose as a result of including tumor treating field electrodes into dose calculation for 10 patients.





**FIGURE 3** | Boxplot of scalp DVH parameters from treatment planning system comparing with and without tumor treating field (TTField) electrodes.

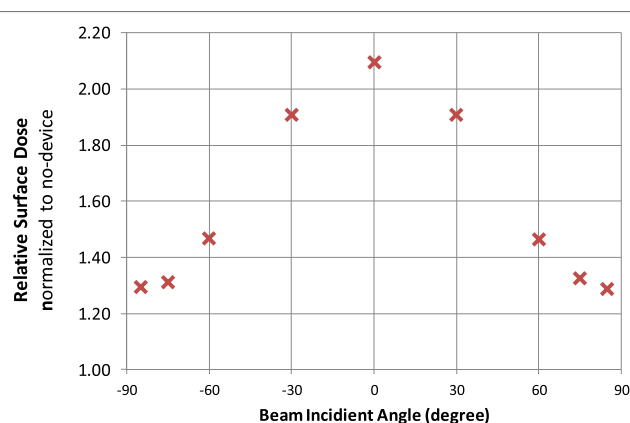
paired dosimetric parameters and the differences between with and without TTFields electrodes indicated were all statistically significant, with  $p$ -values ranging from 0.002 to 0.004.

**Figure 3** shows the distribution of scalp mean dose, D1cc, D10cc, and D20cc of plans calculated with and without taking electrodes into consideration. The impact of the electrodes on the distribution of the scalp DVH parameter is generally small. Doses calculated with electrodes were numerically higher than without, but the paired differences were small although statistically significant.

### Physical Measurements—Surface Dose

**Figure 4** shows the surface dose increase due to the presence of the electrodes. The surface dose measured at different gantry angles were compared to measurement done at the same condition but without the electrodes, and the results were plotted against gantry angles. It is evident that the presence of the TTFields electrode introduced additional buildup effect that increased surface dose directly underneath. This buildup effect was the most pronounced at gantry 0, i.e., beam being perpendicular to the surface, causing surface dose to be 2.1 times measurement without TTFields electrodes. At large angles, i.e., beam being near tangent to the surface, the buildup factor is smaller, but still increases the surface dose underneath the electrode by approximately 30%.

**Figure 5** shows the surface dose measurement comparison for five VMAT plans (12 VMAT arcs) with and without TTFields electrodes. In all cases, the presence of TTFields electrodes significantly increased the surface dose measured by parallel plate



**FIGURE 4** | Surface dose increase factors plotted for different beam incident angles. Factors are normalized to the measurement taken at the same gantry angle without the electrodes.

chamber, by a mean ratio of 2.2 (range, 1.7–2.6), which was a larger effect than was measured in the open beam condition.

### Physical Measurements—Deep Dose

Deep dose measurements for all five patients' plans were shown in **Figure 6**. Regions around the center of the panels showed negative dose deviations, which corresponded to the locations that was shadowed by the TTFields electrodes. The pattern of the cold regions align well with the distribution of the individual electrodes

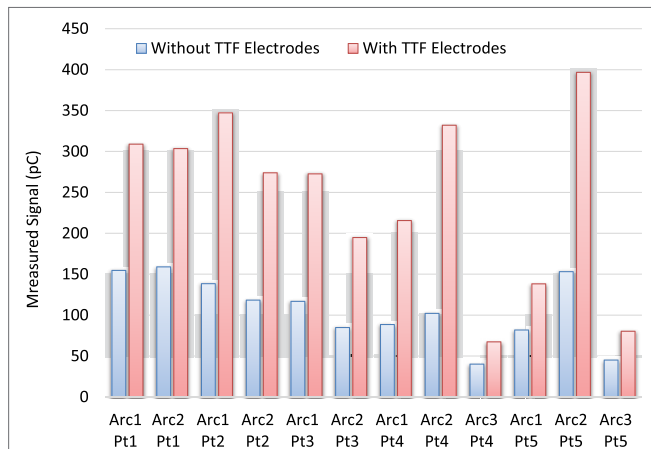


on the TTFields device. Most regions affected by TTFields electrodes showed a dose decrease of 1–2%. Because the radius of the phantom is similar to that of an adult's head, the impact on deep

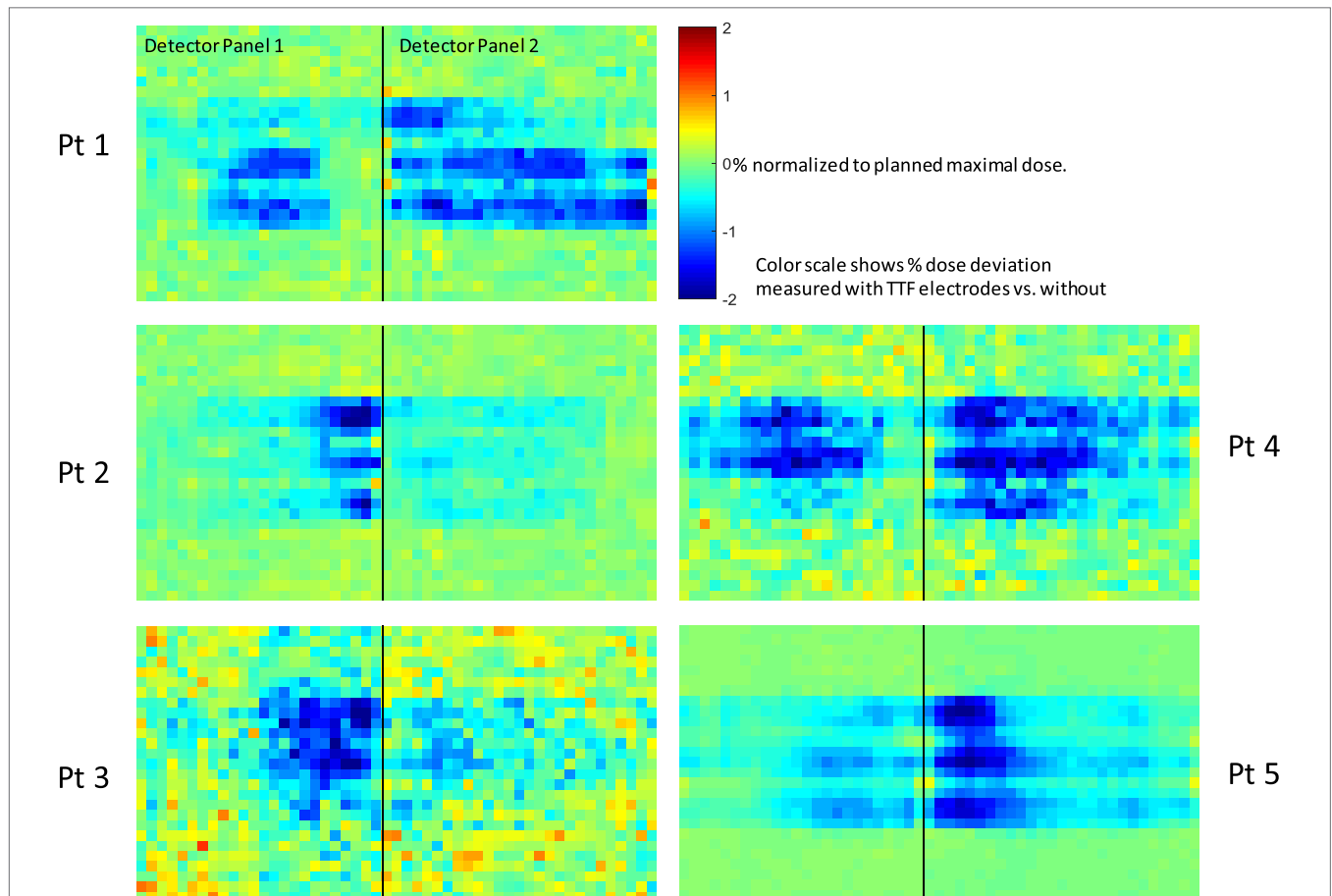
dose in a clinical scenario where patient receives treatment with TTFields electrodes is likely to be in the similar range.

## DISCUSSION

Tumor treating fields has been gaining popularity in recent years as a treatment option for glioblastoma after completion of standard postoperative chemoradiation. In the clinical trials showing efficacy of TTFields, patients were prescribed to wear the device for greater than 18 h daily; this is not always feasible for patients. Utilizing the device in the setting of 6 weeks of daily radiation treatments may increase the logistical challenges to achieving high levels of compliance. From a clinical trial design standpoint, removing and replacing the electrodes on a daily basis to accommodate radiation may confound the outcome and increase skin irritation, since the electrodes are typically exchanged every 2–3 days. As such, before embarking on a trial to evaluate the possible synergy of these treatment modalities, it is necessary to quantify the impact of these high-density electrodes on the dosimetry of radiation treatment. The present work provides radiation oncologists and physicists some quantitative guidelines on how to safely design treatment plans for the delivery of concurrent therapy.



**FIGURE 5** | Surface dose comparison for volumetric-modulated-arc-therapy deliveries for 12 arcs and 5 patients. On average, the ratio of surface dose between measurement with tumor treating field (TTFields) electrodes and the one without is 2.23.



**FIGURE 6** | Deep dose measurement conducted using Delta4™ quality assurance device. Black line separates the two measurement planes orthogonally arranged in the cylindrical phantom. Pixels are color coded according to the dose difference relative to the maximal dose in the plan. The scales are from –2% (deep blue) to +2% (deep red).



The results demonstrate that the presence of TTFields electrodes has minimal impact on the deep dose to the planning target volume, which suggests that tumor dose would be unlikely to be compromised due to shadowing from the electrodes. Importantly, the physical deep dose changes measured in the phantom agreed with the dosimetric changes, which is reassuring.

This dosimetric and physical dose measurement agreement was not seen in the quantification of skin dose. While no significant increase was observed in the treatment planning system using commonly evaluated DVH parameters such as scalp D1cc, physical measurements of surface dose increased when the electrodes were adhered to the surface by a factor of 1.3–2.6 in open field and VMAT deliveries. This result shows that additional caution must be taken into account for skin dose increase, which might not be evident in the DVH evaluation process. Scalp sparing could be improved by using a 3 mm contraction ring from the skin surface with additional penalizing constraints during VMAT optimization. The detailed effectiveness and trade-offs for using this technique is currently under investigation.

The results also provided an important guideline for the design of radiation treatment plans for treating glioblastoma patients concurrently with the TTFields device. Due to the increased dose measured at the surface, some effort to spare the scalp may be clinically meaningful. Further, scalp dose constraints may need to be more conservative, in anticipation of the additional skin dose below the electrodes. While the toxicity rates will have to be measured prospectively, a conservative recommendation might be to limit skin dose during treatment planning between 30 and 50% of published dose constraints.

There are several limitations of the current study. First, only one dose calculation algorithm was used in the planning study. For other dose calculation algorithms and treatment planning systems, the difference between calculated dose with and without TTFields electrodes could be different, especially for the surface dose. Treatment planning systems have long had difficulty with accurate estimation of surface dose. However, as dose calculation algorithms improve, the accuracy of calculated skin/scalp dose is likely to be closer to measurements and may provide a more accurate skin dose estimation during treatment planning.

Second, although a parallel plate chamber was selected to ensure that dose is only measured at a very small depth (~1 mm), the measurement is limited by the large area of parallel plate chamber in the direction parallel to the surface. This limitation can partially explain why VMAT deliveries had a higher surface dose increase than the largest increase found in open field delivery. The ionization chamber used in this study has an active collection volume with a diameter of ~1 cm, while VMAT deliveries consist of many small and rapidly changing fields and segments. For deliveries without TTFields electrodes on top of the chamber window, when the chamber volume is partially exposed to a VMAT segment, only charges generated in the partial volume are collected but averaged over the entire volume. This results in a partial volume effect, which leads to an under-response with VMAT deliveries. When TTFields electrodes were placed on top of the parallel plate chamber's

collection volume, they served to act as a buildup material. In the same small segment scenario described above, even though only a part of the chamber is exposed to primary photons, secondary electrons generated from the TTFields electrodes can still be scattered into the part of collection volume that is not exposed to the primary photon fluence. This effectively increases the parallel plate chamber's collection efficiency under the partial volume condition, which compensates for the partial volume effect and reduces the detector's under-response. When the ratios between measurement with and without TTFields electrodes were calculated, the smaller denominator as a result of more pronounced partial volume effect could make the calculated ratio larger than actual value measured with a true point dose measurement.

When measuring deep dose, the TTFields electrodes were arranged to be in the same plane as the beam's central axis of rotation. This maximized the likelihood of the electrodes being in the beam path. Therefore, the deep dose impacts detected in the above measurements likely represents a "worst case scenario." In an actual clinical setting with patients wearing TTFields electrodes, the arrangement of TTFields electrodes will be non-coplanar and more random due to self-replacement by the patients, and the dosimetric impact is likely to be less than what was observed in the present work.

It is also important to note that the TTFields electrodes patches are disposable and regularly changed by patients. As the location of the electrodes will vary over the duration of RT, an effective averaging of the skin dose hot spots will be observed, which may reduce the maximal skin doses seen in any given region of the scalp. However, due to the uncertainty of this "hot spot averaging," and in the absence of prospective data in patients, the authors recommend conservative scalp dose guidelines in clinical trials, with utilization of methods to reduce scalp dose as much as possible.

## CONCLUSION

In this study, the impact from TTField electrodes on the dosimetry of VMAT treatment plans for patients with glioblastoma was quantitatively evaluated in two ways: (1) in the treatment planning system using advanced dose calculation algorithm and (2) using physical measurements on surface and deep doses. In general, the presence of electrodes decreases deep dose by ~1–2% confirmed by both treatment planning dose calculation and physical measurements. Skin dose underneath the electrodes at ~1 mm depth were measured to be 1.3 – 2.6 times the dose measured without the electrodes, representing an increase by 30% to 160%; this effect was not evident from evaluation of scalp DVH parameters in the treatment planning system. The present work provides evidence that radiation doses to planning target volumes is not significantly changed due to the presence of TTFields electrodes, although the impact on skin dose was notable. As clinical trials to evaluate the potential synergy between TTFields and cranial irradiation are developed, care should be taken during treatment planning to reduce maximum scalp and skin doses well below published guidelines to reduce the risk of potential toxicity.



## ETHICS STATEMENT

The retrospective study was based on data with IRB approval.

## AUTHOR CONTRIBUTIONS

TL contributed to the study design, data acquisition, data analysis, and led manuscript writing. GS contributed to the clinical aspect of study design and manuscript writing. CP and

VL contributed to treatment plan generation. HL contributed to study design and data collection. WS is the PI of this project and provided overall guidance.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Application of tumor treating fields for newly diagnosed glioblastoma: understanding of nationwide practice patterns

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## Abstract

**Background** Tumor treating fields (TTF) harness magnetic fields to induce apoptosis in targeted regions. A 2015 landmark randomized phase III trial of newly diagnosed glioblastoma (GBM) patients demonstrated TTF + temozolomide to be superior to temozolomide alone. Given these results, we sought to assess practice patterns of providers in TTF utilization for GBM.

**Methods** A survey was administered to practices in the United States self-identifying as specializing in radiation oncology, medical oncology, neuro-oncology, neurosurgery, and/or neurology. Responses were collected anonymously; analysis was performed using Fisher's exact test.

**Results** A total of 106 providers responded; a minority (36%) were in private practice. Regarding case volume, 82% treated at least six high-grade gliomas/year. The provider most commonly certified to offer TTF therapy to GBM patients was the neuro-oncologist (40%), followed by the radiation oncologist (34%); 31% reported no TTF-certified physician in their practice. TTF users were more likely to have high volume, and be aware of TTF inclusion in National Comprehensive Cancer Network (NCCN) guidelines ( $p < 0.05$ ).

**Conclusions** More than 80% of TTF for GBM in the United States is performed by groups who treat at least six high-grade gliomas per year; unfortunately more than 30% were in practices bereft of anyone certified to offer TTF therapy. These results indicate that there remains fertile soil for TTF therapy nationwide to be introduced into practices for GBM treatment. Providers seeking to refer newly diagnosed GBM patients for TTF should seek out practices with TTF user-associated characteristics to ensure optimal access for their patients.

**Keywords** Glioblastoma · Tumor treating fields · Neuro-oncology · Radiation oncology · National comprehensive cancer network guidelines

## Introduction

Tumor treating fields (TTF) are a low-intensity, intermediate-frequency, non-invasive and regional antimitotic treatment that harnesses magnetic fields to induce apoptosis in targeted regions [1]. In recurrent glioblastoma (GBM), a phase III trial demonstrated TTF as superior to active chemotherapy with regard to toxicity/quality of life, and comparable with regard to overall survival; this finding led to the approval of TTF for recurrent GBM by the Food and Drug Administration (FDA) in 2011 [2, 3]. Less than 4 years later, interim analysis of a phase III trial of newly diagnosed GBM patients found TTF + temozolomide superior to temozolomide alone in both overall survival and progression-free survival, leading to FDA approval of TTF for newly diagnosed GBM as well as the adoption of TTF in the 2016 National

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Comprehensive Cancer Network (NCCN) guidelines [3, 4]. Given these findings, we sought to assess practice patterns and trends of providers in the utilization of TTF for GBM in the United States.

## Methods

A survey designed through the Oregon Clinical and Translational Research Institute and approved by the Oregon Health and Science University Institutional Review Board was administered in 2017 to practices in the United States which self-identified as specializing in radiation oncology, medical oncology, neuro-oncology, neurosurgery, and/or neurology. The survey was designed and hosted by Research Electronic Data Capture (REDCap), and contained screening questions to ensure respondents were currently practicing and not in training [5]. 2483 physicians were contacted by email and invited to complete the survey.

Responses were collected anonymously; the survey was constructed to identify characteristics of each respondent's typical practice patterns and to assess responder knowledge of appropriate clinical scenarios for TTF, knowledge of TTF therapy status on current NCCN guidelines, and personal approaches for patients with recurrent GBM. Demographic questions included the practicing status of the physician, profession, description of practice setting, year of completed residency/fellowship training, number of physician-partners in immediate practice group/department, region of practice, number of high-grade gliomas treated per year, and the presence of a certified TTF therapy provider. Based on responses, participants were categorized as "users" or "nonusers" of TTF for newly diagnosed GBM. Utilization of TTF was correlated with practice patterns using Fisher's exact test.

## Results

A total of 106 providers responded; 95% were practicing physicians, most commonly representing Missouri (8.9%), Massachusetts (7.9%), California (6.9%), Pennsylvania (5.9%), Oregon (5.9%), and Illinois (5.9%). The most common responders were radiation oncologists (75%) and neuro-oncologists (22%); medical oncologists (3%) and neurosurgeons (1%) comprised the remaining responders. The average number of physician-partners in a responder's practice group was 7.6; a minority (36%) were in private practice. 81% of responders were aware that TTF therapy is listed on current NCCN guidelines; the remaining responders were unaware.

With regard to case volume, only 18% treated 0–5 high-grade gliomas per year, while 24% treated 6–10 annually,

and 58% treated at least 10 high-grade gliomas annually. The provider most commonly reported as certified to offer TTF therapy to GBM patients was the neuro-oncologist (40%), followed by the radiation oncologist (34%); 31% reported no physician in their practice being certified to administer TTF therapy (Fig. 1).

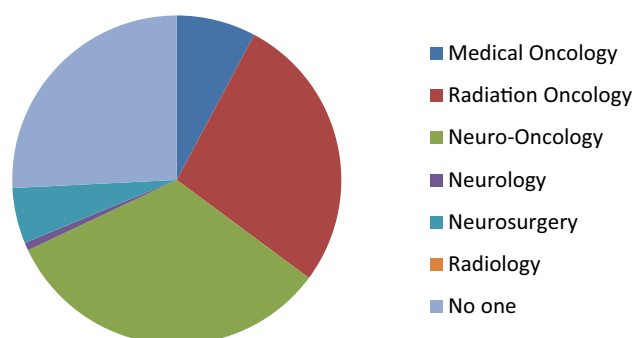
Users of TTF were more likely to have greater high-grade glioma volume ( $> 10$  GBM patients/year;  $p = 0.024$ ; relative risk 1.5), be knowledgeable of TTF inclusion on the 2016 NCCN guidelines ( $p < 0.0001$ ; odds ratio = 10.4; relative risk = 3.0), and specialize in radiation oncology or neuro-oncology ( $p = 0.016$ ) (Table 1). There was no difference in years of practice, location of training, geographic location of practice, number of physician-partners in immediate practice, or academic versus private practice setting between users and nonusers of TTF.

## Discussion

With the most recent evidence firmly in support of TTF plus temozolomide increasing median overall survival in newly diagnosed GBM by 4.9 months over temozolomide alone (more than a 30% increase in life span), it is becoming more imperative for TTF to be made available to GBM patients [6]. We sought to assess the nationwide trends and practice patterns of TTF application in the United States.

Our results indicate that TTF for newly diagnosed GBM in the United States is administered by providers who are knowledgeable of its inclusion in the 2016 NCCN guidelines, have elevated high-grade glioma volume, and specialize in radiation oncology or neuro-oncology. Knowledge of TTF inclusion in the 2016 NCCN guidelines roughly tripled the likelihood of TTF utilization for newly diagnosed GBM, and GBM volume of at least 10 patients/year increased the

**Certified to offer TTF for GBM patients**



**Fig. 1** Depiction of subspecialties certified to offer tumor treating fields (TTF) for glioblastoma (GBM)



**Table 1** Association between clinical practice variables and use versus non-use of tumor treating fields (TTF) for newly diagnosed glioblastoma (GBM)

Clinical demographic	Clinical practice variable	TTF nonuser	TTF user	P value
Practice setting	Academic	18 (58.1%)	46 (65.7%)	0.462
	Private practice	13 (41.9%)	24 (34.3%)	
GBM patients treated yearly	Fewer than 10	19 (61.3%)	23 (32.9%)	0.024
	10 or more patients	12 (38.7%)	47 (67.1%)	
Number of physician-partners in immediate practice	0–4	16 (51.6%)	26 (37.1%)	0.484
	5–9	8 (25.8%)	23 (32.9%)	
	10+	7 (22.6%)	18 (25.7%)	
Subspecialty	Radiation oncology	27 (87.1%)	48 (68.6%)	0.016
	Medical oncology	2 (6.5%)	1 (1.4%)	
	Neuro-oncology	2 (6.5%)	20 (28.6%)	
	Neurological surgery	0 (0%)	1 (1.4%)	
Years of independent practice	0–4	3 (9.7%)	12 (17.1%)	0.112
	5–9	4 (12.9%)	16 (22.9%)	
	10–19	7 (22.6%)	22 (31.4%)	
	20+	17 (54.8%)	20 (28.6%)	
Awareness of TTF therapy on National Comprehensive Cancer Network (NCCN) guidelines	Yes	17 (54.8%)	65 (92.9%)	<0.001
	No	14 (45.2%)	5 (7.1%)	

likelihood of TTF utilization by roughly 50%. Despite widespread implementation of TTF, there remains a substantial portion of medical practices (31%) unable to offer TTF as a treatment modality to GBM patients, and 1/5 of providers remain unaware of the inclusion of TTF in the NCCN guidelines for newly diagnosed GBM. Furthermore, because more than 80% of TTF is performed by groups who treat at least six high-grade gliomas per year (with nearly 60% performed by groups treating more than 10 high-grade gliomas/year), it becomes increasingly imperative for GBM patients to be referred towards high-volume centers to optimize their likelihood of being offered TTF as a treatment modality. This becomes problematic when examining the racial and socioeconomic realities of brain tumor patients, as poor and nonwhite patients are the least likely to be referred to high-volume centers for neuro-oncologic care [7, 8].

Limitations of this study include its low response rate, given that only 106 of the 2483 physicians contacted chose to participate (4.3% response rate); this is unfortunately similar to low response rates reported in studies involving other subspecialties [9]. Because responses were in the format of multiple choice, the full range of opinions may not have been adequately captured. Third, survey fatigue can result in responses that are not genuine; we sought to curb this by not offering an incentive (financial or otherwise) to complete the survey that we hope maximized the rate of legitimate responses. Finally, an important consideration is the lack of granularity in addressing the socioeconomic and racial demographic of patients, the latter of which may impact the applicability of randomized controlled trials comprised of

inadequately low nonwhite patient participation, as has been recently noted in localized prostate cancer [10, 11].

In conclusion, the vast majority of TTF for GBM in the United States is administered by neuro-oncologists and radiation oncologists, usually in an academic setting involving 7–8 physician-partners. However, one-fifth of providers were unaware of TTF therapy being listed on current NCCN guidelines for GBM treatment, and more than 30% were in practices bereft of anyone certified to offer TTF therapy. These results indicate that opportunities exist for TTF therapy nationwide to be introduced into practices for GBM treatment. Given the continued promising results of TTF for newly diagnosed and recurrent GBM in clinical trials thus far, this opportunity should be seized energetically [6, 12]. Providers seeking to refer newly diagnosed GBM patients for TTF should seek out practices with multiple characteristics (i.e. high volume, NCCN guideline inclusion knowledge, radiation oncologist or neuro-oncologist, etc.) to ensure optimal TTF access for their patients.

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### Compliance with ethical standards

**Conflict of interest** Dr. Mitin receives research funding from Novocure. No other author has any conflicts of interest.

**Ethical approval** All studies involving human participants were in accordance with the ethical standards of the institutional research committee.



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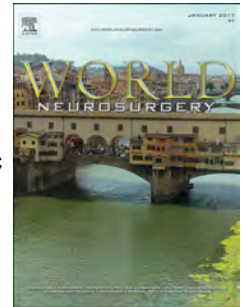
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# Accepted Manuscript

Tumor Treating Fields Utilization in a Glioblastoma Patient with a Preexisting Cardiac Pacemaker: The First Reported Case

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Title:

**Tumor Treating Fields Utilization in a Glioblastoma Patient with a Preexisting Cardiac Pacemaker: The First Reported Case**

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**Abstract**

**Background:** Tumor treating fields (TTF) have become an important, evidence-based modality in the treatment of glioblastoma (GBM). In patients requiring cardiac pacemakers, TTF therapy is complicated by theoretical concerns regarding possible electrical interaction between the devices.

**Case Description:** A 57-year-old man with past medical history of sick sinus syndrome requiring cardiac pacemaker implantation suffered an acute neurologic change associated with a left parieto-occipital lesion, which was found to be GBM. After completion of guideline-concordant chemoradiation, he chose to undergo TTF therapy. Because of the absence of cardiac symptoms and the theoretical risk of far-field sensing by the pacemaker of the TTF device (potentially resulting in pacemaker inhibition), the pacemaker was turned off prior to receiving TTF. Following TTF implementation, the patient responded well; he remains alive more than 25 months following his GBM diagnosis, exceeding the median 20.9 month survival of the recently completed phase III TTF randomized clinical trial for newly diagnosed GBM. Furthermore, he has exhibited neither cardiac morbidity nor adverse scalp reactions to TTF therapy.

**Conclusions:** The first reported case of successful TTF administration in a GBM patient with a previously implanted cardiac pacemaker may allay the concerns of neuro-oncologists, cardiologists, radiation oncologists, and all certified TTF prescribers regarding the applicability of TTF in suitable candidates with preexisting cardiac pacemakers. This case indicates that TTF therapy may be efficacious in patients with indwelling MRI-conditional cardiac pacemakers turned to the off position, and that physical removal of the pacemaker is not necessary prior to starting TTF.



## Introduction

Conclusion of a recent phase III trial has demonstrated that tumor treating fields (TTF) significantly improve overall survival and progression-free survival in glioblastoma (GBM), which has led to its approval by the Food and Drug Administration (FDA), its adoption in the National Comprehensive Cancer Network Guidelines, and its increasing utilization throughout the United States (1-3). For GBM patients with cardiac comorbidity necessitating pacemaker placement, TTF therapy (Optune; Novocure Ltd., St. Helier, United Kingdom) presents certain considerations which may make practitioners reluctant to recommend its utilization. The first is the theoretical risk of electrical interference between the TTF current and the cardiac pacemaker, as indicated on the Optune website: "Optune has not been tested in people with implanted electronic devices, which may cause the devices not to work properly". The second consideration is the perceived inability to use MRI guidance (secondary to the presence of the pacemaker) for planning of the TTF cranial grid array prior to treatment initiation. We report on a patient with a previously implanted cardiac pacemaker who successfully underwent TTF therapy for GBM.



### Illustrative Case

Our patient was a 57-year-old man with a medical history of sick sinus syndrome for which he underwent a dual chamber bipolar pacemaker (Medtronic A2DR01 Advise DR MRI pulse generator with two Medtronic 5076 CapSureFix Novus leads – one atrial and one ventricular; Medtronic, Inc., Minneapolis, MN) implantation in 2015. Unlike older pacemaker models, this model is MRI-conditional, approved by the FDA for 1.5T and 3T full body MRI scan based on the results of a 2015 randomized trial (4).

Shortly afterwards, the patient suffered an acute onset of cognitive changes for which he was brought to the hospital. Although head CT was negative for hemorrhage, brain MRI revealed a left medial temporal lesion and hippocampal cerebritis. Following stabilization, he received operative neurosurgical intervention, which revealed anaplastic astrocytoma. Postoperatively, he declined both radiation therapy (RT) and systemic chemotherapy and decided to pursue alternative treatment. Unfortunately, four months later, he returned to the emergency room with headaches and weakness. Imaging revealed midline shift and a left parieto-occipital recurrent lesion. He underwent a second resection, which revealed GBM (vimentin positive, p53 positive, IDH1 positive, Ki-67 10-20%). Postoperatively, he was referred to radiation oncology and neuro-oncology, and underwent both RT and systemic temozolomide, completing RT two months after surgery. Two months later, he was seen in follow-up in Radiation Oncology clinic and elected to pursue TTF therapy.

Because of the theoretical risk of far-field sensing by the pacemaker of the TTF device, which could potentially have resulted in pacemaker inhibition, the patient underwent a testing session involving cardiologic monitoring, where the pacemaker was confirmed to be turned off (to OOO mode). The patient tolerated this procedure well, as he was in his own native rhythm. He understood that we could



not be certain that there would be no interference between the TTF and pacemaker, and elected to proceed with TTF despite this known risk.

Following TTF implementation, the patient continued primarily with concomitant systemic temozolomide, as he was unable to tolerate bevacizumab. At last follow-up in our multidisciplinary RADIANS (RADiation oncology And NeuroSurgery) multidisciplinary clinic, he remains alive more than 26 months following his GBM diagnosis, exceeding the median 20.9 month survival of the TTF + temozolomide group in the final analysis of the recently completed phase III randomized clinical trial (1, 5). Furthermore, he has exhibited no adverse scalp reactions to TTF therapy nor any cardiac morbidity. Such an excellent response despite receiving no GBM therapy besides temozolomide is indicative that he suffered no defects in the functionality of his TTF device despite the presence of his cardiac pacemaker.



## Discussion

The clinical application of an electrical device to a patient with a preexisting cardiac pacemaker is not a novel concept, as it has successfully been achieved safely and efficaciously in patients requiring deep brain stimulation (DBS) electrode implantation for treatment of medically refractory Parkinson's disease since 2004 (6-7). The greatest theoretical risk is inappropriate shock due to electrical interference (8). This has been seen in reports of cardiac pacemaker discharge at the time of implantation in a patient with preexisting DBS leads, most frighteningly manifesting as microwave diathermy along the path of the DBS lead in a patient, resulting in permanent diencephalic and brainstem lesions concomitant with a vegetative state (9). Another report detailed a patient who underwent a radiofrequency-coupled thalamic stimulator system with an external pulse generator and transmitter; unfortunately, the subcutaneous receiver transmitted the external cardioversion current, resulting in a thalamotomy and the spread of the current to the ventrocaudal nucleus resulting in a central pain syndrome (10). Given such cautionary tales, it is understandable for practitioners to be reluctant to recommend patients with preexisting pacemakers and newly diagnosed GBM having completed concomitant chemoradiation for TTF therapy.

In our patient, open communication between the radiation oncology and cardiology teams regarding TTF in the setting of his pacemaker allowed for a smooth execution of treatment planning where the pacemaker was turned off prior to TTF initiation. Given our patient's underlying cardiac disease (sick sinus syndrome), cardiology believed there was no significant risk of turning his pacemaker off; this estimation has been proven correct by the fact that the patient has demonstrated no cardiac events in the nearly two years since his pacemaker was turned off and has responded very well to TTF. No additions to our patient's baseline cardiology follow-up were recommended by the cardiology team during TTF therapy.



This case brings to mind the obvious question regarding the applicability of TTF therapy for GBM patients with pacemakers that cannot be turned off and the optimal strategy in these situations. Similarly complex scenarios have been published previously involving interactions between DBS electrodes and cardiac pacemakers (6-7). In the seminal report, a preoperative testing session was performed where programming of a test DBS model was performed in the proximity of the patient to evaluate any interaction with their pacemakers utilizing EKG monitoring (6). As in that report, the pacemaker in this patient was a “demand” pacemaker, typical of the vast majority of modern-day implanted pacemakers, which are bipolar in configuration (6). Bipolar devices involve the dipole used for sensing to be located within the heart; this is in contrast to unipolar devices in which the dipole is located between the heart and the pacemaker generator in the chest. For a unipolar device, the metal encapsulating the pacemaker in the chest is electrically active (participating in the sensing circuit), while for a bipolar device metal in the chest is excluded from the sensing circuit because that circuit is composed of the dipole in each lead in the heart, as the anode and cathode are on the lead itself (6). Because the bipolar configuration is less susceptible to oversensing, we believe that bipolar leads are preferable in all cases. Since the bipolar configuration senses within the heart rather than between the heart and the chest wall, the bipolar configuration is less likely to sense extraneous signals. In this patient population, we would recommend that the treating cardiologist maintain bipolar programming; if the cardiologist believes that unipolar programming is required, testing should be performed to rule out TTF device-induced oversensing. Noteworthy is that for patients with pacemakers not compatible with MRI, the cranial grid array mapping for TTF can be performed using CT imaging. Additionally, many centers will perform clinically indicated MRIs on patients with “legacy” i.e. non-MRI conditional pacemakers (11). We would recommend that for patients with more severe cardiac pathology than our patient that cardiology document the cardiac risk per year of turning the pacemaker off, which could



then be compared to the survival benefit of TTF for GBM; depending on the results, cardiology follow-up during TTF therapy may need to be intensified.

In conclusion, our experience with the first manuscript reporting successful TTF administration in a GBM patient with a previously implanted MRI-conditional cardiac pacemaker may allay the concerns of neuro-oncologists, cardiologists, radiation oncologists, and all certified TTF prescribers regarding the applicability of TTF in suitable candidates with preexisting cardiac pacemakers; noteworthy is a previous abstract which described TTF for GBM in three unspecified patients with indwelling pacemakers of unclear specifications and follow-up of unspecified duration (12). This case indicates that TTF therapy may be efficacious in patients with indwelling cardiac pacemakers turned to the off position, and that physical removal of the pacemaker is not necessary prior to starting TTF.

#### **Compliance with Ethical Standards**

Funding: This study received no funding

Ethical approval: All studies involving human participants were in accordance with the ethical standards of the institutional research committee.

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**Highlights:**

1. MRI-conditional cardiac pacemakers do not preclude tumor treating fields (TTF)
2. TTF is efficacious for glioblastoma patients with indwelling pacemakers turned off
3. Physical removal of an indwelling pacemaker is not necessary prior to starting TTF



TTF = Tumor Treating Fields

RADIANS = RADiation oncology And NeuroSurgery

GBM = glioblastoma

FDA = Food and Drug Administration

RT = Radiation Therapy



## Tumour Treating Fields (TTFs) for recurrent and newly diagnosed glioblastoma multiforme

Farhan A. Mirza, Muhammad Shahzad Shamim

### Abstract

In the last decade, significant advances have been made in Glioblastoma Multiforme treatment with the novel use of alternating electrical fields, also termed as tumour treating fields (TTFs). This modality has shown promising results in recurrent and newly diagnosed GBM patients, and according to some, may soon be considered an addition to the previously known 'trifecta' of GBM standard of care, i.e., surgery, chemo and radiation therapy. Here we review the existing data on TTF for both recurrent and newly diagnosed GBM. This review does not discuss the limitations of TTF, especially from compliance and cost point of view.

**Keywords:** Glioblastoma, Tumour Treating Fields, Alternating Electric Fields, Progression Free Survival, Overall Survival

### Introduction

In the first in vivo study involving Tumour Treating Fields (TTF) was tested in ten patients with recurrent GBMs using non-invasive transducer arrays attached to the scalp, with significant improvement noted in time to tumour progression (TTP) [26.1 vs 9.5 weeks], progression free survival (PFS) at 6 months [50% vs 15.3%], and overall survival (OS) [median 62.2 vs 29.3 weeks], without any systemic toxicity.<sup>1</sup> In 2009, the same group performed a second pilot trial to understand the efficacy of TTFs in newly diagnosed patients in combination with standard adjuvant TMZ, and again noted very promising results (Median PFS [155 vs 31 weeks] and improved median OS [> 39 vs 14.7 months]).<sup>2</sup>

### Review of Evidence

We queried the PubMed database with the phrases 'tumour treating fields in glioblastoma' and 'alternating electric fields in brain tumours'.

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**Figure:** An example of TTF applied on a patient.<sup>13</sup>

Abstracts of articles describing this treatment modality were reviewed. Articles addressing use of tumour treating fields in high grade gliomas were reviewed.

### Role in Recurrent GBM

Median time to recurrence for GBM is approximately seven months and median survival 15-18 months. Repeat craniotomy and Bevacizumab have shown to be beneficial in the recurrent setting.<sup>3</sup> Despite this, about 60% of patients relapse on Bevacizumab, can have serious side effects, develop resistance to the drug, and also fail to respond to any further chemotherapy.<sup>4</sup>

In 2012, Stupp et al published their results on the first Phase III trial of 237 patients studying the effects of TTFs alone, compared with standard chemotherapy



regimens in recurrent GBM.<sup>5</sup> Thirty-six patients received bevacizumab, 36 received nitrosureas, 12 received temozolomide, and 33 received other agents. It was noted that TTFs alone were comparably effective and had lower toxicity profile and better quality of life. This landmark study led to the FDA approval of NovoTTF-100A™ System (Novocure, Ltd., Haifa, Israel) as stand alone treatment for recurrent GBMs. Subsequently several post-hoc analyses of this trial were conducted which showed subsets of patients in whom TTFs alone resulted in improved OS compared to second line chemotherapy (11.8 vs 9.2 months).<sup>6</sup> Rulesh et al, in 2012, published their series of twenty patients with recurrent GBM who had been treated with TTFs between 2004 and 2007.<sup>7</sup> They reported four long term survivors who were still alive at the time of publication. According to the authors, this was the first clinical study to have looked at the use of TTFs in recurrent GBM. However, the data reported on the original patients was quite limited and molecular characteristics of tumours in the survivors were not elucidated, hence not many conclusions can be drawn from it. Two trials are currently for recurrent GBM refractory to bevacizumab, and bevacizumab naive recurrent GBM.<sup>8,9</sup>

### Role in Newly Diagnosed GBM

Stupp et al published their first randomized control trial on this subject in 2015.<sup>10</sup> In this study, they used TTFs in combination with maintenance TMZ and compared this group with standard TMZ administration. 695 patients from 83 centers across the world were included between July 2009 and November 2014. Significant improvement in progression free survival and overall survival was noted: 7.1 months (95% CI, 5.9-8.2 months) in the TTF plus TMZ group and 4 months (95% CI, 3.3-5.2 months) in the TMZ alone group. P= 0.001. Median overall survival was 20.5 months (95% CI, 16.7-25.0 months) in the TTF plus TMZ group and 15.6 months (95%CI, 13.3-19.1 months) in the TMZ group P= 0.004). Given this improvement in survival, it has been suggested to include this as part of standard of care for newly diagnosed GBM, in addition to the Stupp Protocol.<sup>11</sup>

In non-methylated MGMT promoter, TMZ is not considered a treatment option due to its resistance. A recent study by Clark et al effectively showed the utility of TTFs in both methylated and non-methylated cells.<sup>12</sup> As such, in patients with non-methylated MGMT promoter, the application of TTFs after radiation should be effective. It is also

interesting to note that tumour cells may develop some resistance to TTFs.

### Conclusion

The introduction and popularization of tumour treating fields is a remarkable development in GBM treatment since the introduction of the Stupp protocol in 2005. It offers an entirely new area for research and possible options for treatment. So far, studies have shown promising results with this treatment modality, with the added benefit of minimal toxicity and improved quality of life compared to standard chemoradiation options.

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## Article

# Alternating Electric Fields (TTFields) Activate Ca<sub>v</sub>1.2 Channels in Human Glioblastoma Cells

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**Abstract:** Tumor treating fields (TTFields) represent a novel FDA-approved treatment modality for patients with newly diagnosed or recurrent glioblastoma multiforme. This therapy applies intermediate frequency alternating electric fields with low intensity to the tumor volume by the use of non-invasive transducer electrode arrays. Mechanistically, TTFields have been proposed to impair formation of the mitotic spindle apparatus and cytokinesis. In order to identify further potential molecular targets, here the effects of TTFields on Ca<sup>2+</sup>-signaling, ion channel activity in the plasma membrane, cell cycle, cell death, and clonogenic survival were tested in two human glioblastoma cell lines in vitro by fura-2 Ca<sup>2+</sup> imaging, patch-clamp cell-attached recordings, flow cytometry and pre-plated colony formation assay. In addition, the expression of voltage-gated Ca<sup>2+</sup> (Ca<sub>v</sub>) channels was determined by real-time RT-PCR and their significance for the cellular TTFields response defined by knock-down and pharmacological blockade. As a result, TTFields stimulated in a cell line-dependent manner a Ca<sub>v</sub>1.2-mediated Ca<sup>2+</sup> entry, G<sub>1</sub> or S phase cell cycle arrest, breakdown of the inner mitochondrial membrane potential and DNA degradation, and/or decline of clonogenic survival suggesting a tumoricidal action of TTFields. Moreover, inhibition of Ca<sub>v</sub>1.2 by benidipine aggravated in one glioblastoma line the TTFields effects suggesting that Ca<sub>v</sub>1.2-triggered signaling contributes to cellular TTFields stress response. In conclusion, the present study identified Ca<sub>v</sub>1.2 channels as TTFields target in the plasma membrane and provides the rationale to combine TTFields therapy with Ca<sup>2+</sup> antagonists that are already in clinical use.

**Keywords:** glioma; alternating electric field therapy; Ca<sup>2+</sup> signaling; programmed cell death; clonogenicity; L-type Ca<sup>2+</sup> channel; benidipine

## 1. Introduction

Tumor Treating Fields (TTFields) therapy, developed by the company NovoCure (Haifa, Israel) is a new modality of anti-cancer therapy which has been FDA-approved for newly diagnosed and recurrent glioblastoma multiforme and is currently evaluated for several other tumor entities. TTFields apply alternating intermediate-frequency (200 kHz) sine wave-electric fields with low field strength (1–3 V/cm) to the tumor with the help of non-invasive ceramic transducer electrode arrays (for glioblastoma patients mounted on the shaved scalp). TTFields were usually administered 20–24 h/day



for several months [1] concomitantly to temozolomide maintenance therapy after surgical resection of the glioblastoma and subsequent radiochemotherapy with temozolomide. A phase III clinical trial on recurrent glioblastoma comparing TTFields monotherapy with physician's choice chemotherapy indicates that the efficacy of TTFields is similar to chemotherapy with improved toxicity profile [1]. The 6-year-follow-up of a prospective randomized multicenter phase III trial on newly diagnosed glioblastoma comparing standard temozolomide maintenance therapy with standard therapy plus TTFields electrotherapy indicates a significant improvement of progression-free and overall survival by TTFields [2]. Importantly, the adverse side effects of TTFields therapy are restricted to mild to moderate skin rash beneath the transducer arrays [1,3]. Combined these clinical data indicate that TTFields electrotherapy is an effective and safe treatment modality for glioblastoma patients increasingly offered to patients in good performance status willing to wear the electrode arrays.

TTFields reportedly target mitosis and cytokinesis [4–7]. Mechanistically, TTFields have been proposed to align proteins possessing high intramolecular dipole moments such as tubulin dimers [6] and septins [7] which counteracts proper formation of the mitotic spindle apparatus and positioning of the cytokinetic furrow, respectively. In addition, dielectrophoretic forces in areas of non-uniform TTFields as proposed to occur at the cytokinetic furrow within the dividing cells have been postulated to trap polar macromolecules and organelles and to impair their symmetrical distribution between daughter cells. As a consequence, TTFields induce aberrant metaphase exit, improper chromosome segregation and mitotic catastrophe eventually resulting in cell death [8].

By inhibiting mitosis and cytokinesis, TTFields in particular target fast proliferating cells which results in a certain tumor specificity. Not surprisingly, besides glioblastoma, several other tumor entities such as skin, breast, pancreatic, lung, and ovarian cancer have been reported to react on TTFields in vitro [5–7,9–14], in preclinical in vivo models [5,9,12,13,15–17] or in clinical pilot studies [9,18–20]. Notably, best, i.e., most effective TTFields frequency and field strength differ between the different tumor entities with a best frequency of 200 kHz for glioblastoma [4,9,21].

Beyond impairment of mitosis and cytokinesis, TTFields reportedly lower metastatic spread of tail vein-injected B16 melanoma cells [15], and sensitize to chemo- [10], targeted [22], or radiation therapy [23]. The latter probably results from TTFields-mediated delay in DNA double strand break repair [23] possibly via downregulation of BRCA1 signaling [14]. Importantly, immunosuppression by dexamethasone seems to attenuate the response of glioblastoma patients to TTFields therapy [24] illustrating the function of the immune system in the tumor control by TTFields. Combined, these data point to a complex biological response to TTFields therapy.

Therefore, the present study aimed to identify molecular TTFields targets beyond the proposed mitotic spindle apparatus or the cytokinesis furrow. Such novel targets might be used as markers for patient stratification in terms of therapy personalization. In addition, the identification of novel molecular pathways that are triggered by TTFields and that confer resistance against the electric field therapy bears the great chance for pharmacological intervention and amplification of TTFields efficacy.

Our study placed emphasis on  $\text{Ca}^{2+}$  signaling and  $\text{Ca}^{2+}$ -regulated cellular processes such as cell cycle or cell death since alternating electrical fields have been demonstrated to interfere with intracellular  $\text{Ca}^{2+}$  signals. For instance, voltage-activated  $\text{Ca}^{2+}$  ( $\text{Ca}_v$ ) channels in the electrosensory organs of sharks are involved in perception of changes in the environmental electrical fields [25]. Likewise in mammalian cells, experimental or environmental alternating electric fields have been demonstrated to evoke intracellular  $\text{Ca}^{2+}$  signals [26–32] that may involve in particular L-type  $\text{Ca}_v$  channels in the plasma membrane (for review see [33–35]). The alpha subunits of the L-type  $\text{Ca}^{2+}$  channels  $\text{Ca}_v1.1$ ,  $\text{Ca}_v1.2$ ,  $\text{Ca}_v1.3$ , and  $\text{Ca}_v1.4$  are encoded by the *CACNA1S*, *-1C*, *-1D*, and *1F* gene, respectively. While  $\text{Ca}_v1.1$  is mainly expressed in the skeletal muscle and  $\text{Ca}_v1.4$  restricted to retina,  $\text{Ca}_v1.2$  and  $\text{Ca}_v1.3$  are expressed in most excitable cells. In brain,  $\text{Ca}_v1.2$  and  $\text{Ca}_v1.3$  are found in the dendrites and soma of neurons where among others they are involved in the excitation-transcription coupling [36]. Notably,  $\text{Ca}_v$  channels are also expressed by glioblastoma cells [37]. Potential downstream targets of  $\text{Ca}_v$  are  $\text{Ca}^{2+}$ -activated high conductance  $\text{BK}_{\text{Ca}}$  [38–41] and intermediate



conductance  $IK_{Ca}$  ( $K_{Ca3.1}$ , SK4)  $K^+$  channels [42–44] that have been reported to contribute to cell migration or therapy resistance of glioblastoma cells. Hence, here we analyzed TTFields-evoked modulation of cytosolic free  $Ca^{2+}$  concentration ( $_{free}[Ca^{2+}]_i$ ) and  $Ca^{2+}$ -dependent ion channel activity in the plasma membrane in individual human glioblastoma cells with the help of a single cell TTFields applicator disclosing a TTFields-stimulated  $Ca^{2+}$  entry that involves  $Ca_v1.2$  channels. In a second step, effects of TTFields on cellular DNA content, mitochondrial membrane potential ( $\Delta\Psi_m$ ) and colony formation were analyzed in dependence on pharmacological  $Ca_v$  blockage with the help of a TTFields cell culture applicator in order to assess cell cycle distribution, asymmetric cell division, cell death, triggering of intrinsic apoptosis, and clonogenic survival.

## 2. Materials and Methods

### 2.1. Cell Culture and Transfection

Human T98G (obtained from American Type Cell Culture Collection (ATCC, Manassas, VA, USA) and U251 (kindly provided by Dr. Luiz Penalva, San Antonio, TX, USA) glioblastoma cells were grown in 10% fetal calf serum (FCS)-supplemented RPMI-1640 (T98G) or DMEM (4500 mg glucose/L, U251) medium. For CACNA1C knock-down, exponentially growing U251 and T98G cells were reversely transfected with a mixture of three Stealth siRNAs (Thermo Fischer Scientific, Waltham, MA, USA) specific for human CACNA1C (HSS187849, HSS187850, HSS187851) or with nt siRNA (*Silencer*®Select Negative Control No. 1 siRNA, #4390844, Ambion™, Thermo Fischer Scientific). Detached T98G and U251 cells (250,000 in 2.5 mL RPMI-1640/10% FCS and DMEM (4500 mg glucose/L)/10% FCS medium, respectively) were added to 500  $\mu$ L of pre-incubated (20 min at room temperature) Opti-MEM medium containing RNAiMAX lipofectamine (6  $\mu$ L, Invitrogen Life Technologies, Carlsbad, CA, USA) and siRNA (25 nM final concentration).

### 2.2. Fura-2 Fluorescence Imaging of Cytosolic Free $Ca^{2+}$ Concentration ( $_{free}[Ca^{2+}]_i$ )

Fluorescence measurements were performed at 37 °C using an inverted phase-contrast microscope (Axiovert 100; Zeiss, Oberkochen, Germany). Fluorescence was evoked by a filter wheel (Visitron Systems, Puchheim, Germany)-mediated alternative excitation at 340/26 or 387/11 nm (AHF, Analysentechnik, Tübingen, Germany). Excitation and emission light was deflected by a dichromatic mirror (409 nm beam splitter, AHF) into the objective (Fluar 40 $\times$ /1.30 oil; Zeiss) and transmitted to the camera (Visitron Systems), respectively. Emitted fluorescence intensity was recorded at 587/35 nm (AHF). Excitation was controlled and data acquired by Metafluor computer software (Universal Imaging, Downingtown, PA, USA). The 340/380-nm fluorescence ratio was used as a measure of  $_{free}[Ca^{2+}]_i$ . Control, CACNA1C- or nt siRNA-transfected T98G and U251 cells (48 h after transfection) were incubated with fura-2/AM (2  $\mu$ M for 30 min at 37 °C; Molecular Probes, Goettingen, Germany) in RPMI-1640/10% FCS and DMEM/10% FCS medium, respectively.  $_{free}[Ca^{2+}]_i$  was recorded at 37 °C during superfusion with  $Ca^{2+}$ -containing NaCl solution (in mM: 125 NaCl, 32 HEPES, 5 KCl, 5 D-glucose, 1  $MgCl_2$ , 1  $CaCl_2$ , titrated with NaOH to pH 7.4), with  $Ca^{2+}$ -free NaCl solution (in mM: 125 NaCl, 32 HEPES, 5 KCl, 5 D-glucose, 1  $MgCl_2$ , 0.6 EGTA, titrated with NaOH to pH 7.4), or with  $Ca^{2+}$ -containing NaCl solution further containing the L-, N-, T-type  $Ca^{2+}$  channel blocker benidipine or the L-type inhibitor nifedipine (both 1  $\mu$ M, Sigma-Aldrich, Taufkirchen, Germany) before, during and after application of TTFields (200 kHz, 0–2.5 V/cm).

### 2.3. Patch Clamp Recording

Currents of semi-confluent T98G and U251 cells were elicited by 33 voltage square pulses (700 ms each) delivered in 5 mV increments from 0 mV holding potential to voltages between –80 mV and +80 mV and recorded at 37 °C in cell-attached, voltage-clamp mode by an EPC-9 amplifier (Heka, Lambrecht, Germany) using Pulse software (Heka) and an ITC-16 Interface (Instrutech, Port Washington, NY, USA).



Clamp voltages refer to the intracellular face of the plasma membrane. Flow of positive charge out of the cells (or the counter flow of anions) is defined as positive current and depicted as upward deflection of the current tracings. Cells were superfused at 37 °C with  $\text{Ca}^{2+}$ -containing NaCl solution (see above). Borosilicate glass pipettes (4–6 M $\Omega$  pipette resistance; GC150 TF-10, Clark Medical Instruments, Pangbourne, UK) manufactured by a microprocessor-driven DMZ puller (Zeitz, Augsburg, Germany) filled with  $\text{Ca}^{2+}$ -containing NaCl solution (see above) were used in combination with a STM electrical micromanipulator (Lang GmbH and Co KG, Hüttenberg, Germany). Macroscopic cell-attached currents were analyzed by averaging the currents between 100 and 700 ms of each square pulse. In addition to macroscopic cell-attached currents unitary current transitions were characterized for single channel conductance and open probability ( $P_o$ ). The latter was estimated by subtracting the zero current (i.e., the current at no apparent unitary current transition) at a given clamp voltage from the averaged macroscopic current and by dividing the difference by the amplitude of the unitary current transition and by the apparent number of active channels.

#### 2.4. Quantitative RT-PCR

RNA of control, CACNA1C siRNA-, or nt siRNA-transfected U251 and T98G cells (48 h after transfection) was isolated (NucleoSpin<sup>®</sup> RNA kit, Machery-Nagel, Düren, Germany) and reversely transcribed and CACNA1A, -1B, -1C, -1D, -1E, -1G, -1H, -1I, -1S as well as housekeeper  $\beta$ -actin (ACTB)-, pyruvate dehydrogenase beta (PDHB)-, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH)-specific fragments were amplified by the use of SYBR Green-based quantitative real-time PCR (1Step RT qPCR Green ROX L Kit, highQu, Kraichtal, Germany, and QuantiTect Primer Assays QT00054152, QT00077042, QT00053480, QT00076657, QT00063994, QT00043043, QT00075159, QT00021126, QT00000833, QT00095431, QT00031227, Qiagen, Hilden, Germany) in a Roche LightCycler<sup>®</sup> 480 Instrument (Roche, Mannheim, Germany). mRNA abundances were normalized to the geometrical mean abundance of the three housekeepers.

#### 2.5. Analysis of Cell Cycle, DNA Degradation and Aneuploidy

Exponentially growing T98G and U251 cells were treated for 5–7 days with TTFields (200 kHz, 1 V/cm) in the presence of benidipine (0 or 1  $\mu\text{M}$  in 0.1% DMSO), trypsinized, washed, and stained (30 min at room temperature) with propidium iodide (PI, Sigma-Aldrich) in RNase-containing phosphate-buffered saline (PBS) further containing 0.1% Na-citrate, 0.1% triton X-100, and PI (10  $\mu\text{g}/\text{mL}$ ). For cell cycle analysis, DNA amount was recorded by flow cytometry (FACS Calibur, Becton Dickinson, Heidelberg, Germany, 488 nm excitation wavelength) with FL-3 (>670 nm, linear scale) emission wavelength. In addition, DNA content was monitored with FL-2 emission wavelength (585/42 nm, log scale) for determination of sub-G<sub>1</sub> (DNA degradation) and hyper-G (aneuploidy) populations, respectively. Data were analyzed with the FCS Express 3 software (De Novo Software, Los Angeles, CA, USA).

#### 2.6. Determination of Inner Mitochondrial Membrane Potential ( $\Delta\Psi_m$ )

TTFields-treated (5–7 days, 200 kHz, 1 V/cm) and benidipine-co-treated (0 or 1  $\mu\text{M}$  in 0.1% DMSO) T98G and U251 cells were trypsinized, washed, and incubated for 30 min at room temperature in  $\text{Ca}^{2+}$ -containing NaCl solution (see above) containing the  $\Delta\Psi_m$ -specific dye tetramethylrhodamine ethyl ester perchlorate (TMRE, 25 nM, Invitrogen, Karlsruhe, Germany). TMRE-specific fluorescence was measured by flow cytometry with FL-2 (585/42 nm) emission wavelength.

#### 2.7. Colony Formation Assay

To test for clonogenic survival, T98G and U251 were pre-plated (600 cells/well in 12-well plates), co-incubated with benidipine (0 or 3  $\mu\text{M}$  in 0.3% DMSO) and subjected to TTFields (200 kHz, 1 V/cm) for 5–7 days and further grown for 10–14 days in the continuous presence of benidipine. Thereafter, clusters of  $\geq 50$  cells were defined as colonies and counted manually after fixation and Coomassie



staining. The plating efficiency was defined by dividing the number of colonies by the number of plated cells. Survival fractions were calculated by dividing the plating efficiency of the TTFields-treated cells by those of the TTFields-untreated vehicle controls. Survival fractions were calculated by dividing the plating efficiency of the TTFields-treated cells by those of the TTFields-untreated vehicle controls.

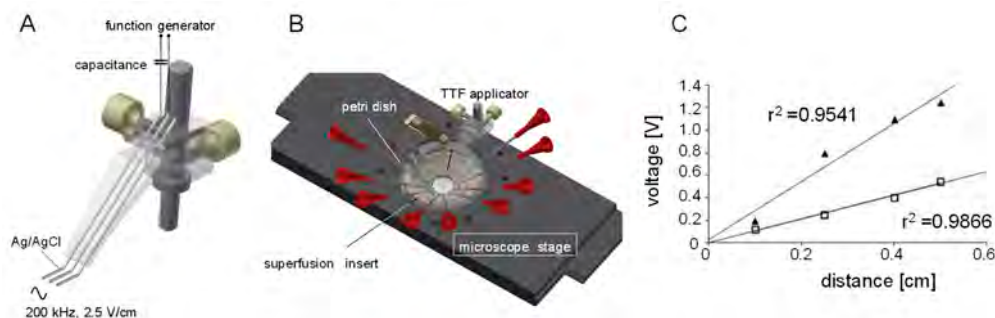
## 2.8. Statistics

Data are given as means  $\pm$  standard error (SE). Probability ( $p$ ) of statistical significance was estimated with two-tailed Student's  $t$ -test. A  $p$ -value of  $\leq 0.05$  (2 samples) or  $\leq 0.05/n$  (2 samples) was assumed to be significant where  $n$  = number of pair wise comparisons in multiple testing (Bonferroni correction).  $n$  = number of pair wise comparisons in multiple testing (Bonferroni correction).

## 3. Results

### 3.1. Results

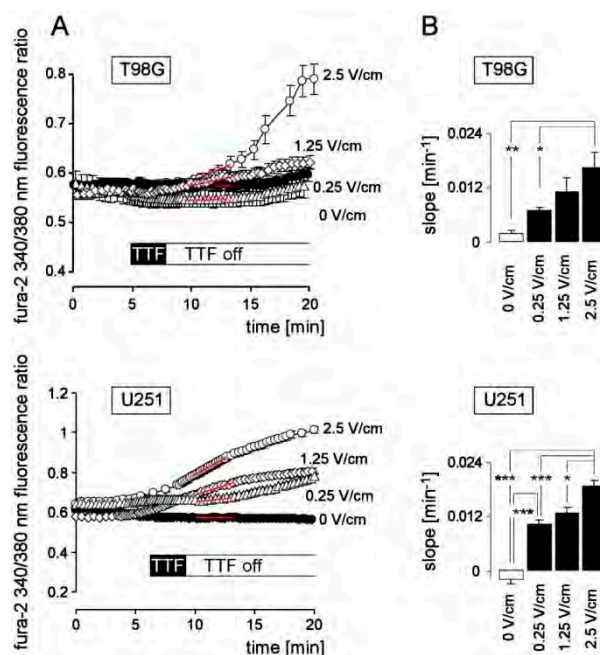
To identify molecular TTFields targets, a TTFields single cell applicator (Figure 1) was constructed. To identify molecular TTFields targets, a TTFields single cell applicator (Figure 1) was constructed, and TTFields single cell applicator. Attached to the stage of an inverted microscope, the TTFields single cell applicator allowed application of electric fields across parallel variable amplitude and frequency to individual cells. TTFields were applied parallel to the plane of the cell layer (active conductive junctions (as applied Ag/AgCl electrodes) is that, in the only difference situation possible, TTFields injection (as applied to the patients) is that bathing solution is not possible. The electrical stimulation may, additionally, in the bathing solution, predominantly of the cells (the solution interface). Total ion exchange is prevented by constant superfusion of the cells that guaranteed fast bath solution exchange. The frequency of 0.25–2.5 V/cm was set to 200 kHz. In the bath solution, the output adjusted to electric field strength of 0.25–2.5 V/cm measured in the bath solution between the two electrodes (Figure 1C).



**Figure 11.** Single cell TTFields applicator. (A) Drawing of the applicator. TTFields are applied conductively by two Ag/AgCl electrodes connected via a capacitance (to avoid flow of offset direct current) to a function generator (37 Hz). (B) Positioning of the TTFields applicator. Petri dish, superfusion insert, heating insert, stage of an inverted microscope. TTFields application and cell recording were performed at 37 °C during continuous superfusion with bath solution. Field strength in the bath solution between both application electrodes at the dish bottom was controlled by the use of two Ag/AgCl recording electrodes. (C) Recorded voltages (peak to peak) within the TTFields at different distances. TTFields field strength was adjusted to 2.5 V/cm (closed triangles) and 1.1 V/cm (open squares) in NaCl solution, respectively. Recorded voltages were fitted by linear regression. The obtained correlation coefficients ( $r^2$ ) were  $r^2 = 0.9541$  and  $r^2 = 0.9866$ , suggesting a homogeneous distribution of the alternating electric fields between the applicator electrodes.

Since low alternating electric fields have been reported to interfere with intracellular  $\text{Ca}^{2+}$  signaling (see Introduction section), we first assessed TTFields-induced changes in intracellular free  $\text{Ca}^{2+}$  concentration ( $[\text{Ca}^{2+}]_{\text{free}}$ ) by ratio-metric fura-2  $\text{Ca}^{2+}$  imaging. As a result, acute application of TTFields to U251 and U937 and glioblastoma cells induced a long-lasting increase in  $[\text{Ca}^{2+}]_{\text{free}}$  in an electric field intensity (0.25–2.5 V/cm)-dependent manner (Figure 2A,B). In particular,  $[\text{Ca}^{2+}]_{\text{free}}$  continued to rise for more than 10 min after switching off the TTFields stimulation.





**Figure 2.** TTFIELDS induce  $\text{Ca}^{2+}$  signals in U251 and T98G human glioblastoma cells in a dose-dependent manner. (A) Time course of mean ( $\pm$  SE;  $n = 8$ –17) fura-2 340/380 nm fluorescence ratio as a measure of  $[\text{Ca}^{2+}]_i$  recorded in T98G (top) and U251 cells (bottom) during superfusion with 1 mM  $\text{Ca}^{2+}$ -containing NaCl-solution before, during and after application of 0 (control), 0.25, 1.25, or 2.5 V/cm TTFIELDS (200 kHz) field strength for 3 min. (B) Mean ( $\pm$  SE;  $n = 8$ –55) slope (as indicated by red lines in (A)) of the TTFIELDS-induced increase in fura-2 340/380 nm fluorescence ratio as calculated for U251 (left) and T98G (right) cells. \*, \*\*, and \*\*\* in (B) indicate  $p < 0.05$ ,  $p < 0.01$ , and  $p < 0.001$ , respectively, (Welch)-corrected t-test and Bonferroni correction for 6 pairwise comparisons.

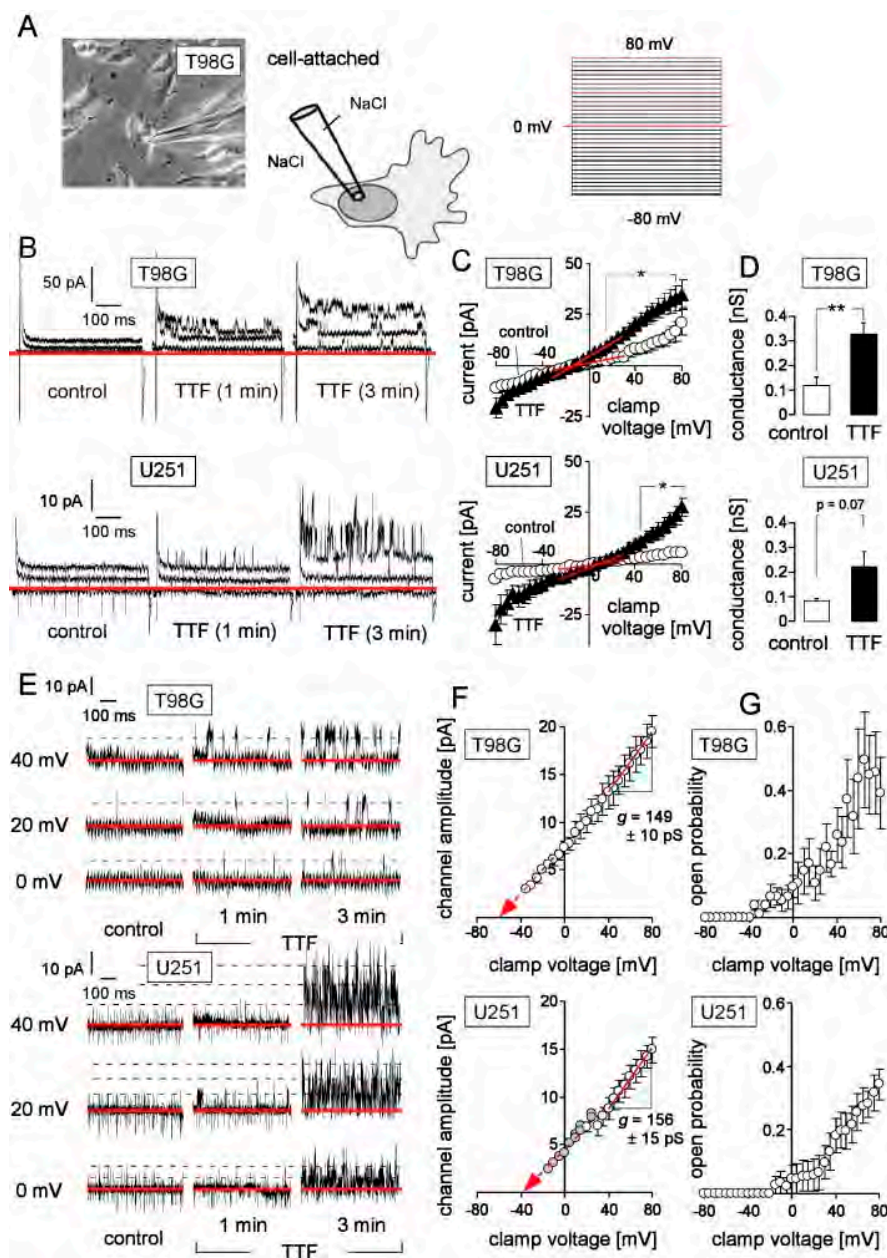
To test for functional significance of this TTFIELDS-induced rise in  $[\text{Ca}^{2+}]_i$ , functionality of  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  channels in the plasma membrane was monitored shortly before and directly after TTFIELDS application (2.5 V/cm for 1–3 min) by continuous cell-attached patch-clamp recording with physiological extracellular NaCl solution in bath and pipette (Figure 3A).

Due to the experimental set-up with an electrical line from the function generator outside the Faraday cage to the TTFIELDS applicator electrodes that were placed closely to the recorded cells inside the Petri dish, a high 50 Hz ripple superimposed the cell-attached currents. This rendered it impossible to resolve unitary current transitions generated by low or intermediate conductance ion channels. However, the “macroscopic” cell-attached currents as a measure of overall channel activity of the channels. However, the “macroscopic” cell-attached currents as a measure of overall channel activity recorded membrane area could be analyzed. As a result, TTFIELDS induced in both glioblastoma lines an instantaneous increase in macroscopic cell-attached outward currents at positive clamp voltages (Figure 3A–C). Moreover, in the range of the physiological membrane potential (i.e., at 0 mV voltage, see below), TTFIELDS increased (T98G cells) or showed a trend to increase (U251) the conductance of the clamped membrane area (Figure 3D) suggesting that TTFIELDS may interfere with the physiological electrosignaling of glioblastoma cells.

Remarkably, the macroscopic currents in Figure 3B (middle, right) disclose large unitary current transitions that could be characterized in more detail (Figure 3E–G). Figure 3E shows in higher power cell-attached current tracings at three clamp voltages (0, +20 and +40 mV) before (left) and after 1 min (middle) or 3 min (right) of TTFIELDS application in T98G (top) and U251 cells (bottom). In both glioblastoma lines, TTFIELDS stimulated the activity of a channel with a conductance in the range of 150 pS as deduced from the channel amplitude/voltage (I/V) relationships in Figure 3F. In addition, the I/V curves in this figure extrapolate (red arrow) to a reversal potential (i.e., where the curve crosses the x-axis) of around -60 mV in T98G cells (Figure 3F, top) and around -40 mV clamp voltage in U251 cells (Figure 3F, bottom). In cell attached mode when recorded with a physiological (i.e., 5 mM  $\text{K}^+$ -containing) NaCl pipette and bath solution, the (negative) physiological membrane



Cancers 2019, 11, 110 voltage in U251 cells (Figure 3F, bottom). In cell attached mode when recorded with a physiological (i.e., 5 mM  $K^+$ -containing) NaCl pipette and bath solution, the (negative) physiological membrane potential remains unaltered and applied on top of the clamp voltage across the recorded membrane. Thus, the actual reversal potentials of the I/V curves in Figure 3F are more negative than those deduced from the clamp voltage. This is important since it suggests that the actual reversal potential of the TTFs-activated channel is close to the highly negative  $K^+$  equilibrium potential indicating its  $K^+$  selectivity.



**Figure 3.** TTFs activate BK  $K^+$  channels. (A) Macroscopic cell-attached currents were recorded from T98G (micrograph on the left) and U251 cells with the patch-clamp technique using a physiological NaCl-rich extracellular solution in bath and pipette (middle). Currents were elicited by 33 square pulses (700 ms each) to voltages between  $-80$  and  $+80$  mV delivered from  $0$  mV holding potential in  $5$  mV increments as shown by the voltage-clamp pulse protocol on the right. (B) Cell-attached current tracings recorded as in (A) from a T98G (top) and a U251 cell (bottom) before (left), after  $1$  min (middle) and  $3$  min (right) TTFs ( $200$  kHz,  $2.5$  V/cm) application. As illustrated by the red lines in the pulse protocol (A right), only currents elicited by voltage steps to  $0$ ,  $+40$  and  $+80$  mV are shown (red lines in (B) indicate the zero current). (C) Relationship between the mean ( $\pm$  SE;  $n = 10$ – $11$ ) macroscopic cell-attached currents and the clamp voltage in control ( $0$  V/cm, open circles) and



5 mV increments as shown by the voltage-clamp pulse protocol on the right. (B) Cell-attached current tracings recorded as in (A) from a T98G (top) and a U251 cell (bottom) before (left), after 1 min (middle) and 3 min (right) TTFields (200 kHz, 2.5 V/cm) application. As illustrated by the red lines in the pulse protocol (A, right), only currents elicited by voltage steps to 0, +40 and +80 mV are shown (red lines in (B) indicate the zero current). (C) Relationship between the mean ( $\pm$ SE;  $n = 10$ –11) macroscopic cell-attached currents and the clamp voltage in control (0 V/cm, open circles) and TTFields (2.5 V/cm)-treated (closed triangles) T98G ( $n = 10$ , top) and U251 cells ( $n = 6$ , bottom). (D) Mean ( $\pm$ SE;) conductance of the clamped membrane area in T98G (top) and U251 cells (bottom) as calculated between  $-30$  and  $+30$  mV clamp voltage from the data in (C, red lines) by linear regression. \* and \*\* in (C, and F, top) indicate  $p \leq 0.05$  and  $p \leq 0.01$ , respectively, Welch-corrected  $t$ -test. The square brackets in (C) mark the voltage range, where control and TTFields-stimulated cell-attached currents differ significantly; the number in (D, bottom) indicates the  $p$  value. (E) Cell-attached current tracings recorded in a T98G (top) and a U251 cell (bottom) at 0, +20 and +40 mV clamp voltage before (control) and after 1 and 3 min of TTFields exposure disclosing TTFields-induced unitary outward current transitions (red lines and dashed lines indicate zero current and distinct current levels of up to three simultaneously open channels, respectively). (E,G) Relationship between channel amplitude (F) and estimated open probability (G) of the unitary current transitions in T98G (top) and U251 cells (bottom). Shown are mean ( $\pm$ SE,  $n = 3$ –5, open symbols) or individual data (grey symbols). The red lines and red arrows in (F) depict the clamp voltage range used to calculate the single channel conductance ( $g$ ) by linear regression and extrapolate to the likely reversal potential, respectively.

An estimation of the open probability ( $P_o$ ) of this high conductance  $K^+$  channel (Figure 3G) further suggests for both glioblastoma lines a depolarization-induced activation of the channel and an increase in its  $P_o$  with increasing positive voltage. Notably, the  $P_o$ /voltage relationship (Figure 3G, bottom) as well as the  $I/V$  curve (Figure 3F, bottom) of U251 cells were shifted by some +20 mV when compared to the situation in T98G cells (Figure 3F,G, top). This can be explained with a higher negative physiological membrane potential in U251 as compared to T98G cells since the higher the physiological membrane potential the more positive clamp voltage is required to reach the activation voltage of the channel. Most importantly,  $K^+$  selectivity, high unitary conductance, and voltage dependence of the TTFields-induced channel were identical to the characteristics of paxilline-sensitive BK  $K^+$  channels reported earlier to be highly expressed in T98G and U251 cells [45].

The  $I/V$  curves in Figure 3C especially in U251 cells also show a trend to TTFields-stimulated inward currents which, however, did not reach statistical significance. The underlying single channel activity could not be resolved because of the above mentioned limitations of our experimental set up. Along those lines, inward current transitions generated by  $Ca^{2+}$  channels such as low conductance voltage-gated L-type channels (e.g., upon depolarization from 0 mV clamp voltage, i.e., from the physiological membrane potential, to +40 mV clamp voltage) could also not be resolved. The same holds true for  $IK_{Ca}$  ( $KCa3.1$ ,  $SK4$ )-mediated outward current transitions. Nevertheless, our observations suggest that the observed TTFields-induced increase in  $free[Ca^{2+}]_i$  is functionally relevant and sufficient to activate BK  $K^+$  channels.

Next, we characterized the TTFields-induced  $free[Ca^{2+}]_i$  rise in further fura-2 experiments by analyzing its dependence on extracellular  $Ca^{2+}$  and its sensitivity to the  $Ca^{2+}$  channel inhibitors benidipine and nifedipine (1  $\mu$ M, both). In both glioblastoma lines, decrease of extracellular  $Ca^{2+}$  by superfusion with  $Ca^{2+}$ -free, EGTA-chelated NaCl solution (Figure 4A) or application of the L-, N-, T-type  $Ca_v$  channel blocker benidipine in  $Ca^{2+}$ -containing superfusate (Figure 4B,C,E) abolished the TTFields-induced rise in  $free[Ca^{2+}]_i$ . In contrast to benidipine, the L-type  $Ca_v$  inhibitor nifedipine abolished only in T98G cells the TTFields-induced  $free[Ca^{2+}]_i$  rise completely while conferring only a partial blockage in U251 cells (Figure 4B,D,E). Notably,  $free[Ca^{2+}]_i$  started to increase for several minutes upon wash-out of benidipine and nifedipine 2 min and 5 min, respectively, after switching off the TTFields stimulation (Figure 4C). Together, those experiments suggest a TTFields-induced  $Ca^{2+}$  entry via the activation of a nifedipine-sensitive L-type  $Ca_v$  channels in T98G and U251 cells and via an



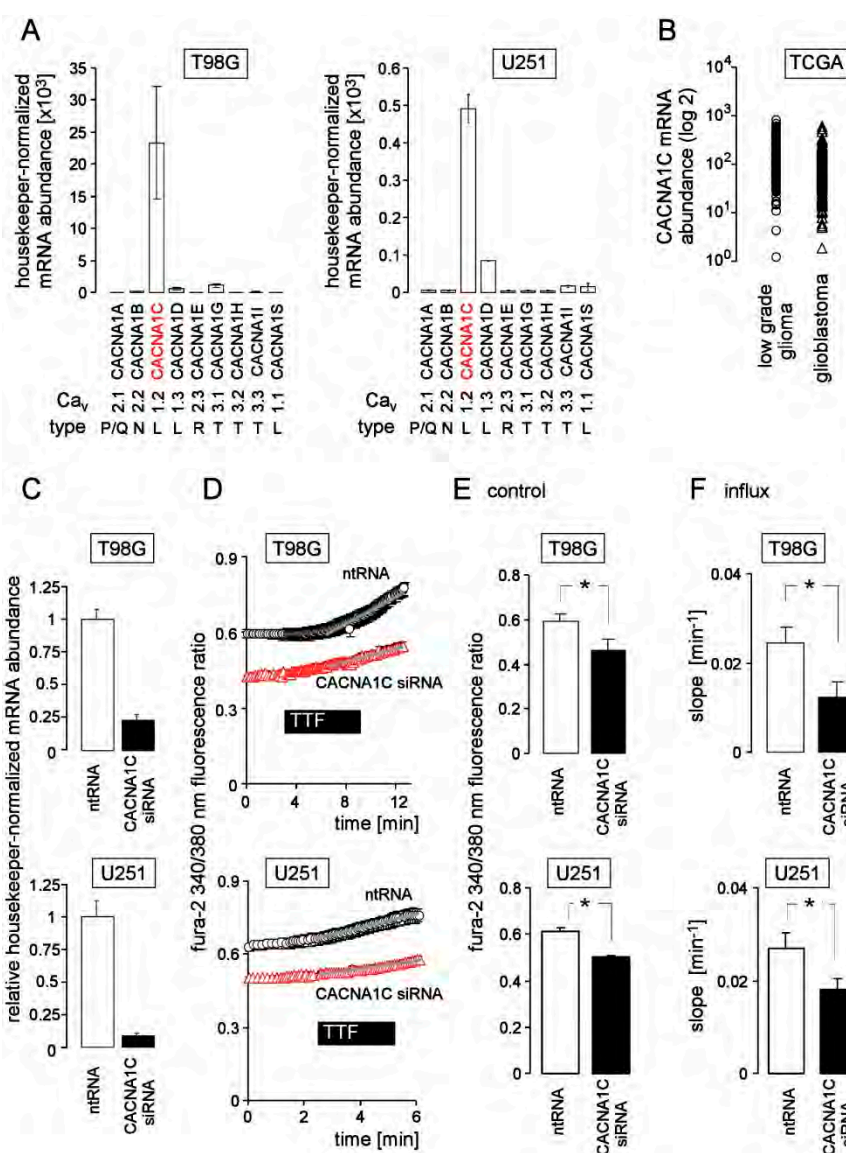




Further on, we analyzed the expression of potential benidipine targets in glioblastoma. To this end, we assessed the abundance of mRNA encoding  $\text{Ca}^{2+}$  channels in our two human glioblastoma cell lines and in glioma resection specimens by RT-PCR and by querying the TCGA low grade glioma and provisional glioblastoma data bases, respectively. Among all tested mRNAs, the mRNA of the L-type channel CACNA1C ( $\text{Ca}_v1.2$ ) was most abundant in T98G and U251 cells (Figure 5A). In T98G, housekeeper-normalized CACNA1C mRNA abundance exceeded that of U251 cells by almost factor of 50. Similarly, CACNA1C mRNA abundance varied considerably in resection specimens of low grade and high grade glioma (Figure 5B). Together, these data suggest CACNA1C is expressed in glioblastoma albeit at variable extent. To test for functional significance of this channel, the effect of CACNA1C knockdown (Figure 5C–F) on control and TTFIELDS-modulated  $\text{free}[\text{Ca}^{2+}]_i$  in T98G and U251 cells was determined by fura-2  $\text{Ca}^{2+}$  imaging. As shown in Figure 5D,E, transfection with CACNA1C siRNA decreased resting  $\text{free}[\text{Ca}^{2+}]_i$  suggesting constitutive activity of  $\text{Ca}_v1.2$  in both cell lines. Moreover, CACNA1C siRNA lowered the slope of the TTFIELDS-induced  $\text{free}[\text{Ca}^{2+}]_i$  rise in T98G and U251 cells (Figure 5D,F) pointing to an involvement of  $\text{Ca}_v1.2$  in here.

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**Figure 5.** The voltage-gated L-type  $\text{Ca}^{2+}$  channel CACNA1C ( $\text{Ca}_v1.2$ ) contributes to the TTFIELDS-induced  $\text{Ca}^{2+}$  entry. (A) Mean ( $\pm$  SE;  $n = 3$ ) housekeeper-normalized mRNA abundances ( $\times 10^3$ ) of P/Q-, N-, L-, R- and T-type  $\text{Ca}_v$  channels CACNA1A, -1B, -1C, -1D, -1E, -1G, -1H, -1I, and -1S (as indicated) in T98G (left) and U251 (right) cells as determined by real-time RT-PCR indicating expression of CACNA1C in both human glioblastoma lines. (B) CACNA1C mRNA abundances (log2 RNA seq) of human low grade glioma (left) and glioblastoma (right) specimens vary considerably between individual tumors. The provisional Glioblastoma-Multiforme and Lower-Grade-Glioma TCGA databases (<http://cancergenome.nih.gov/>) were queried for CACNA1C mRNA abundance in the



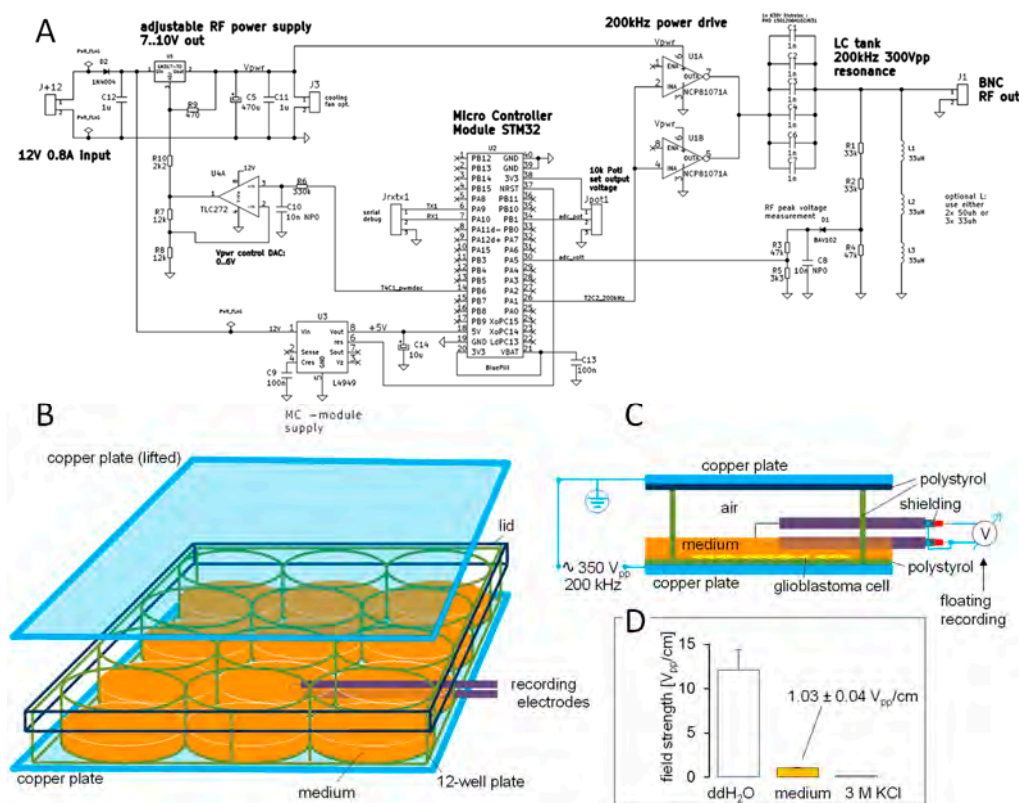
TTFields-induced  $\text{Ca}^{2+}$  entry. (A) Mean ( $\pm$ SE;  $n = 3$ ) housekeeper-normalized mRNA abundances [ $\times 10^3$ ] of P/Q-, N-, L-, R- and T-type  $\text{Ca}_v$  channels CACNA1A, -1B, -1C, -1D, -1E, -1G, -1H, -1I, and -1S (as indicated) in T98G (left) and U251 (right) cells as determined by real-time RT-PCR indicating expression of CACNA1C in both human glioblastoma lines. (B) CACNA1C mRNA abundances (log2 RNA seq data) of human low grade glioma (left) and glioblastoma (right) specimens vary considerably between individual tumors. The provisional Glioblastoma-Multiforme and Lower-Grade-Glioma TCGA databases (<http://cancergenome.nih.gov/>) were queried for CACNA1C mRNA abundance in the tumor specimens via the cBIOportal Web resource [46,47]. (C) Mean ( $\pm$ SE;  $n = 3$ ) relative housekeeper-normalized abundance of CACNA1C mRNA in T98G (top) and U251 (bottom) cells 48 h after reverse transfection with CACNA1C-siRNA (closed bars) or non-targeting RNA (ntRNA, open bars). (D) Mean ( $\pm$ SE;  $n = 6$ –19) fura-2 340/380 nm fluorescence ratio of CACNA1C siRNA (red triangles)- or ntRNA-transfected (open circles) T98G (top) and U251 cells (bottom), before, during and after application of TTFields (200 kHz, 2.5 V/cm, 3–5 min). (E,F) Mean ( $\pm$ SE;  $n = 6$ –19) control ratio (E) and TTFields-induced increase in (F) fluorescence ratio of CACNA1C siRNA (red bars)- or ntRNA-transfected (open bars) T98G (top) and U251 cells (bottom). \* indicates  $p \leq 0.05$ , Welch-corrected  $t$ -test).

To study the interaction of TTFields with cell biology, we developed a cell culture TTFields applicator that applied 200 kHz sine wave electrical fields to a multi-well plate (Figure 6A). The field (1 V/cm peak-to-peak amplitude) was injected perpendicular to the cell layer in a capacitive manner via electrically isolated copper foils mounted below the bottom and above the lid of the multi-well plate (Figure 6B–D). To identify effects of TTFields on cell cycle and the role of  $\text{Ca}_v1.2$  herein, we co-treated T98G and U251 cells for 5–7 days with TTFields (0 or 1 V/cm) and benidipine (0 or 1  $\mu\text{M}$ ) and determined the cellular DNA content by propidium iodide staining in flow cytometry thereafter. In T98G, TTFields showed a tendency to decrease  $G_1$  population and significantly increased S and decreased  $G_2$  populations (Figure 7A top and Figure 7B, upper row) suggestive of a TTFields-induced S phase arrest. Benidipine alone did not affect cell cycle distribution in T98G cells but augmented the TTFields effect on  $G_1$  and S populations (Figure 7A top and Figure 7B, upper row). In contrast, TTFields increased  $G_1$  and decreased  $G_2$  population of U251 cells (Figure 7A bottom and Figure 7B, lower row) indicative of a TTFields induced  $G_1$  arrest. Unlike T98G, benidipine had no effect on cell cycle distribution of U251 cells (Figure 7B, lower row).

To further identify TTFields-caused asymmetric cell division, hyper-G population (i.e., cells with DNA content larger than normal diploid cells) was quantified as a measure of chromosome aneuploidy. In T98G, benidipine tended to elevate and TTFields increased hyper-G population, and both effects seemed to be additive (Figure 7C,D, top each). In U251, by contrast, TTFields tended to decrease hyper-G population while benidipine had no effect (Figure 7C,D, bottom each). Finally, sub- $G_1$  population was analyzed as a measure of dying or dead cells with degraded DNA. In T98G, TTFields and benidipine additively induced cell death (Figure 7E,F, top each). In U251, in contrast, neither TTFields nor benidipine evoked cell death (Figure 7E,F, bottom each).

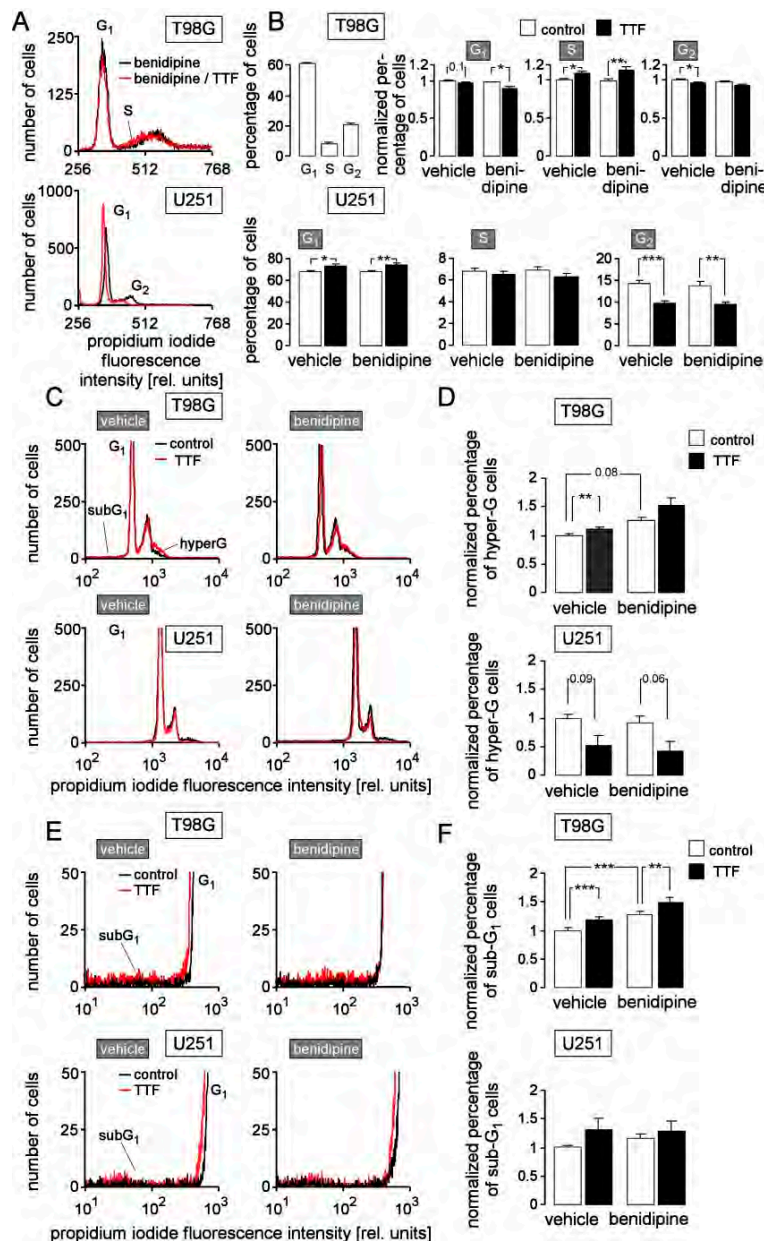
To characterize potential death pathways, we determined the inner mitochondrial membrane potential ( $\Delta\Psi_m$ ) by TMRE staining in flow cytometry in T98G and U251 cells treated with TTFields (0 or 1 V/cm) and benidipine (0 or 1  $\mu\text{M}$ ) using time schedules identical to those applied for cell cycle analysis. In T98G, TTFields showed a trend to induce  $\Delta\Psi_m$  dissipation as indicated by low TMRE staining while benidipine alone had no effect. In combination, however, TTFields and benidipine evoked a doubling of cell population with dissipated  $\Delta\Psi_m$  suggesting their synergistic action (Figure 8A,B top each). In U251, in contrast, TTFields and benidipine in each case alone stimulated  $\Delta\Psi_m$  dissipation (3-fold and 1.5-fold, respectively), effects that were not additive in combined treatment (Figure 8A,B bottom each). Together, these data suggest that TTFields alone (U251) or in combination with benidipine (T98G) may trigger intrinsic apoptosis.





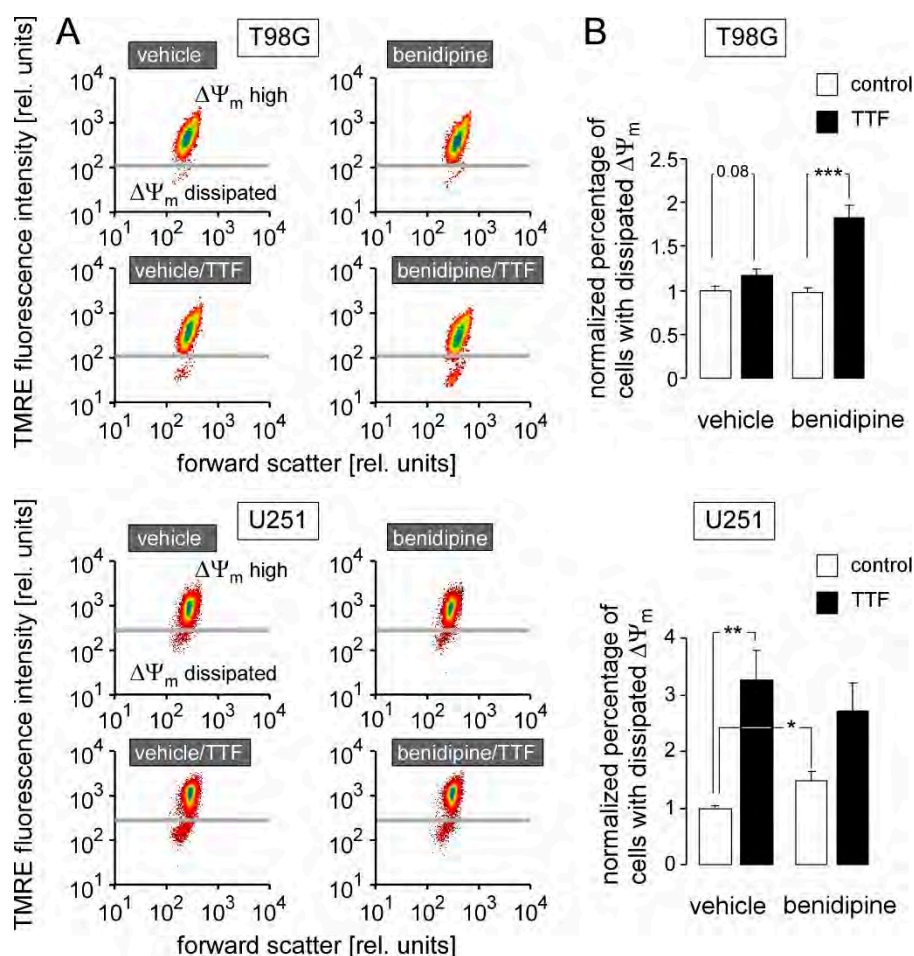
**Figure 6.** Cell culture TFields applicator. (A) Circuitry of applicator. Frequency and amplitude of the 200 kHz, 300 Vpp TFields signal is controlled by a “STM32 blue pill” micro controller module (MCM). Software was developed with the free ARDUINO programming environment. A 200 kHz digital clock is generated by the MCM internal programmable timers. This clock is amplified by a stage that delivers sufficient current and voltage to drive a 200 kHz series LC resonance tank. LC power drive stage that delivers sufficient current and voltage to drive a 200 kHz series LC resonance tank. LC tank resonance transforms the digital 7 to 10 V peak to peak drive signal into a clean sine wave of 200 kHz and up to 350 V peak to peak at the RF output. Amplitude can be set by a potentiometer which controls the supply voltage of the LC-tank power drive. (B–D) Calibration of the applicator. TFields (maximal output) are applied capacitively via two electrically isolated copper foils mounted below and above a 12-well cell culture plate. The electric field strength applying to the cells was determined under the chosen experimental conditions by the use of two shielded electrodes that were inserted laterally in a central well of a 12-well plate measuring chamber filled with 1 ml culture medium in that were inserted laterally in a central well of a 12-well plate measuring chamber filled with 1 ml every well (B,C). For quality control of this measurement, the culture medium of the recorded well was replaced by media with lower (ddH<sub>2</sub>O) and higher (3 M KCl) dielectric constant. As a result, electric field strength (maximal output) in cell culture medium was the range of 1 V/cm. Moreover, decreasing (ddH<sub>2</sub>O) or increasing the permittivity (3 M KCl) increased and decreased, respectively, the electric field strength accordingly (D, data are means ± SE, n = 3–4). In particular, electric field strength in respectively, the electric field strength accordingly (D, data are means ± SE, n = 3–4). In particular, ddH<sub>2</sub>O was about 12-times that of plasma-isotone cell culture medium (D) which suggests a relative dielectric constant of around 1000 for the cell culture medium similar to the value reported for human plasma in this wavelength range [48]. The TFields application (5–7 days) was performed in a normal humidified 37 °C cell culture incubator in 5% CO<sub>2</sub> atmosphere. Continuous TFields application did not increase the temperature of the cultured cells. Temperature recording during up to 24 h of TFields (maximal output) with a thermo-resistor directly placed in the fluid column of the cell-culture well did not disclose any TFields-associated temperature increase (36.4 ± 0.17 °C, n = 5) as compared to control recording in the same set-up with switched-off TFields (36.5 ± 0.07 °C, n = 3).





**Figure 7.** TTF field stimulation at G<sub>1</sub> or G<sub>2</sub> cell cycle arrest in T98G and U251 cells and an increase in hyper-G and sub-G<sub>1</sub> populations at T98G. T98G cells (top) and U251 cells (bottom) treated for 7 days with TTF fields of 0 (black) or 1 V/cm (red) field strength and benidipine (0 or 1  $\mu$ M). (A,C,E) Histograms of flow cytometry showing the DNA content (DNA content with propidium iodide staining) in T98G (top) and U251 (bottom) cells. (B,D,F) Bar graphs showing the percentage of cells in G<sub>1</sub>, S, or G<sub>2</sub> phase of cell cycle (B, upper line, 2nd to 4th bar diagram and lower line, the bar diagram in the upper left gives the absolute values for the control situation in T98G), cells with elevated DNA content (hyper-G population, D), absolute values in the control situation were  $7.0 \pm 0.6\%$  for T98G and  $3.9 \pm 0.5\%$  for U251, and dead cells (sub-G<sub>1</sub> population, F), absolute values in the control situation were  $2.8 \pm 0.3\%$  for T98G and  $0.4\%$  for U251. (E) absolute values in the control situation were  $2.8 \pm 0.3\%$  for T98G and  $0.4\%$  for U251. (F) absolute values in the control situation were  $2.8 \pm 0.3\%$  for T98G and  $0.4\%$  for U251. (B, upper line, 2nd diagram) and (D) indicate  $p$  values.



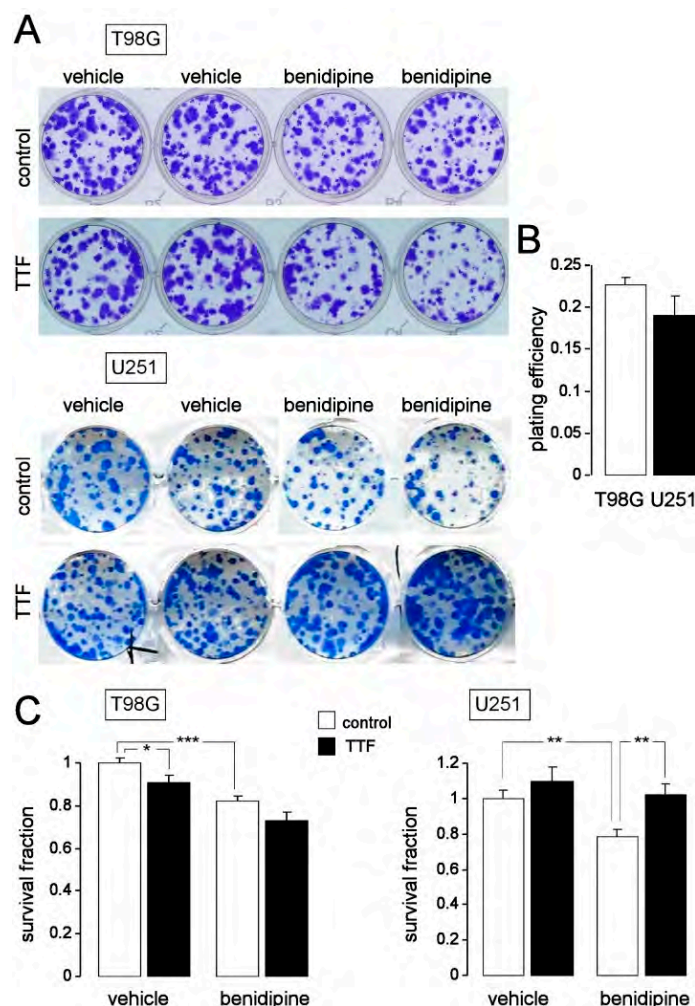


**Figure 8.** Benidipine augments TTFIELDS-induced breakdown of the inner mitochondrial membrane potential ( $\Delta\Psi_m$ ) in T98G cells. (A) Dot plots showing forward scatter and TMRE fluorescence intensity of T98G (top) and U251 cells (bottom) treated for 7 days with 0 (control) or 2.5 V/cm TTFIELDS (200 kHz) in the absence (vehicle) or presence of benidipine (1  $\mu$ M). (B) Mean ( $\pm$  SE;  $n=12-22$ ) normalized percentage of T98G (top) and U251 (bottom) cells with dissipated  $\Delta\Psi_m$  after 5–7 days of treatment with 0 (control) or 1 V/cm TTFIELDS (TTF, 200 kHz) and 0 or 1  $\mu$ M benidipine (absolute values of the control situation were  $4.5 \pm 1.0\%$  for T98G and  $4.3 \pm 1.3\%$  for U251). \*, \*\*, and \*\*\* indicate  $p \leq 0.05$  and  $p \leq 0.01$ , respectively, Welch-corrected *t*-test and Bonferroni correction for three pairwise comparisons (vehicle/control vs. benidipine/control, vehicle/control vs. vehicle/control + TTFIELDS, and benidipine/control vs. benidipine/TTFIELDS). Number in (B, top) indicates *p* value.

Finally, we defined whether or not TTFIELDS-induced cell death may lower clonogenic survival which is the most relevant endpoint in oncology with regard to tumor relapse after therapy. Pre-plating colony formation assay (5–7 days of TTFIELDS with 0 or 1 V/cm and co-incubation with 0 or 3  $\mu$ M benidipine followed by 10–14 days of post-incubation in the continuous presence of benidipine until formation of colonies, Figure 9A,B) suggest that both, TTFIELDS- and benidipine monotherapies, attenuated clonogenic survival of T98G cells. In combination, the effects of both therapies tended to be additive (Figure 9A, top and Figure 9C, left). In U251, in sharp contrast, TTFIELDS rather increased clonogenic survival and abolished the inhibitory effect of benidipine (Figure 9A, bottom and Figure 9C, right). In summary, our experiments suggest that TTFIELDS modulate  $Ca^{2+}$  signaling in two human glioblastoma cell lines which involves long-lasting activation of L-type  $Ca_v1.2$  (CACNA1C) and most probably further  $Ca_v$  channels and which was completely suppressed by  $Ca^{2+}$  channel inhibitor benidipine. Cell line-dependently, TTFIELDS induce S (T98G) or G<sub>1</sub> cell cycle arrest (U251), aneuploidy, and DNA degradation (T98G), triggered intrinsic apoptosis (U251), and decreased clonogenic survival



(T98G). Importantly, in T98G cells which exhibited about 50 times higher CACNA1C mRNA abundance than U251, but not in U251 cells, benidipine aggravated TTFields-triggered cell cycle arrest, intrinsic apoptosis and DNA degradation and showed a tendency to act additively to TTFields on induction of aneuploidy and attenuation of clonogenic survival. In U251, benidipine alone triggered intrinsic apoptosis and decreased clonogenic survival. The latter was reversed by TTFields.



**Figure 9.** TTFields reduce clonogenic survival of T98G but not of U251 cells. (A) Pre-plating colony formation of T98G (top) and U251 (bottom) cells after treatment with 0 V/m (control) or 1 V/m TTFields field strength and co-incubation with vehicle alone or benidipine (1 µM) for 7 days. Shown are cut-outs of 6-well plates with Coomassie-stained T98G (top) and U251 (bottom) colonies. (B) Mean (±SE,  $n = 16-22$ ) plating efficiency of T98G and U251 cells. (C) Mean (±SE,  $n = 16-24$ ) survival fractions of T98G (left) and U251 cells (right) after treatment with 0 V/m (control) or 1 V/m TTFields strength and co-incubation with vehicle alone or benidipine (3 µM) for 7 days. Data were obtained by pre-plating colony formation assay as shown in (A). \* and \*\* indicate  $3p \leq 0.05$ ,  $3p \leq 0.01$ , and  $3p \leq 0.001$ , respectively. Welch-corrected  $t$ -test and Bonferroni correction for three pairwise comparisons (vehicle/control vs. benidipine/control, vehicle/control vs. vehicle/TTFs, and benidipine/control vs. benidipine/TTFs).

#### 4. Discussion

In our study, TTFields impaired clonogenicity of T98G but not of U251 human glioblastoma cells indicating that individual glioblastoma may respond differentially to this electric field therapy. The inhibition of clonogenic survival of T98G cells by 5–7 days of TTFields was below 10%. At a first glance, this effect seems to be too low to become tumor biologically relevant. However, one has to take into account that field direction (perpendicular and not parallel to the cell layer and field strength (1 V/cm instead of 3 V/cm) did not match the reported [4] optimal settings due to technical limitations of our set-up. This might hint to an underestimation of the TTFields effect by our experiments. In addition, overall treatment time of several months might lead to significantly larger effects on



take into account that field direction (perpendicular and not parallel to the cell layer and field strength (1 V/cm instead of 3 V/cm) did not match the reported [4] optimal settings due to technical limitations of our set-up. This might hint to an underestimation of the TTFields effect by our experiments. In addition, overall treatment time of several months might lead to significantly larger effects on glioblastoma cell death and clonogenic regrowth compared to the one week application of TTFields for our in vitro experiments.

The 6-years follow up of the multicentric randomized prospective clinical trial analyzing temozolomide vs. temozolomide plus TTFields maintenance therapy suggests that in particular glioblastoma patients with methylated MGMT (O-6-methylguanine-DNA methyltransferase) promotor in the tumor benefit from TTFields therapy [2]. This might suggest that efficacy of TTFields increases with decrease of MGMT activity. In our experiments, however, the TTFields more responding line T98G has been reported to express higher MGMT activity [49] than the low TTFields responder U251 [50]. Alternatively, one might speculate that TTFields which is applied concurrently to temozolomide maintenance therapy becomes especially effective in MGMT promotor-methylated, temozolomide-sensitive cells pre-damaged by the chemotherapy. As a matter of fact, temozolomide and TTFields have been reported to synergistically accelerate cell death of irradiated glioblastoma cells in vitro, however, independently of MGMT status [51]. Additive anti-proliferative effects of temozolomide and TTFields have also been reported for temozolomide-sensitive and resistant glioblastoma stem cell-enriched primary cultures [52]. Along those lines, TTFields have been shown in vitro to improve the efficacy of radiotherapy in glioblastoma [23] and non small cell lung cancer cells [14] possibly by impairing repair of DNA double strand breaks [14]. Combined, this might suggest that TTFields are especially efficient in combination with other cytotoxic anti-cancer therapies such as radiotherapy or chemotherapy and enhance their effect as has been described for moderate locoregional hyperthermia [53]. As a matter of fact, combining mitotic checkpoint inhibition with TTFields in vitro synergistically enhance apoptotic cell death in glioblastoma cells [54].

The reported interference with DNA repair by TTFields [14] also suggests that TTFields exert additional cellular effects beyond impairment of mitotic spindle formation and cytokinesis as proposed cellular mechanisms of anti-neoplastic TTFields action (see Section 1). Evidence for the latter two came in our study from the TTFields-induced increase in T98G cell population with hyper-G DNA content as a measure of aneuploidy. Beyond that, our study identified benidipine-sensitive  $\text{Ca}^{2+}$  channels that comprise L-type CACNA1C ( $\text{Ca}_v1.2$ ) channels as further TTFields targets. The dihydropyridine calcium channel blocker benidipine acts on L-, T-, and N-type channels. Like in the present study, alternating current electromagnetic fields (ac-EMF) such as microwave or Wi-Fi have been demonstrated in several independent studies to activate  $\text{Ca}^{2+}$  entry pathway in various cell types. Notably, these pathways were in part sensitive to inhibitors of voltage-gated  $\text{Ca}^{2+}$  channels suggesting that the ac-EMF sensitivity of voltage-gated  $\text{Ca}^{2+}$  channels is a general phenomenon (for review see [33]). Particularly striking was the fact that in our experiments  $\text{Ca}_v$ -mediated  $\text{Ca}^{2+}$  influx outlasted TTFields stimulation by far suggesting a constitutive activity of  $\text{Ca}_v$  channels. As a matter of fact, such constitutive activity has been reported in smooth muscle cells for L-type  $\text{Ca}^{2+}$ -channels. This constitutive activity and functional clustering of channels reportedly are mediated by protein kinase C (PKC) and determine the resting  $_{\text{free}}[\text{Ca}^{2+}]_i$  in these cells [55]. Along those lines, pulsed electrical field induced contraction of feline esophageal smooth muscle cells reportedly requires both, extracellular  $\text{Ca}^{2+}$  and PKC activity [56]. This might suggest that similar processes contribute to the long-lasting  $\text{Ca}^{2+}$  entry in TTFields-treated glioblastoma cells.

Taking into account that cell cycle [57], cell migration [38,45,57], brain infiltration [40], cell death programming [57], DNA repair and radioresistance [42,57] of glioblastoma cells have been demonstrated to be regulated by  $\text{Ca}^{2+}$ -dependent signaling pathways [58] an interference of TTFields with glioblastoma biology can be expected. In line with this assumption, the present study demonstrated that TTFields indeed interfered with all cell biological parameters tested.



Of note, the voltage-gated  $\text{Ca}^{2+}$  channel blocker benidipine did not revert the observed cellular TTFields effects indicating that these effects most probably were not induced by TTFields-triggered benidipine-sensitive  $\text{Ca}^{2+}$  influx. Rather, benidipine aggravated (or showed the tendency to increase) the TTFields effects in T98G cells. Unexpectedly, such a concerted action of benidipine and TTFields was not observed in U251 cells although both glioblastoma lines exhibited comparable TTFields-induced  $\text{Ca}^{2+}$  entries that were both completely blocked by benidipine (see Figure 4). In contrast to T98G, TTFields decreased aneuploidy and rather increased than decreased clonogenic survival in U251 again illustrating that individual glioblastomas may respond differentially to TTFields.

Irrespective of its effect in combination with TTFields, benidipine alone induced in the present study in both glioblastoma lines either DNA degradation (T98G) or  $\Delta\Psi_m$  dissipation (U251) and lowered clonogenic survival (both lines) indicating its anti-neoplastic action. Among the known benidipine targets, mRNA encoding the L-type  $\text{Ca}^{2+}$  channel CACNA1C ( $\text{Ca}_v1.2$ ) was most abundant in both glioblastoma lines strongly suggesting that the observed benidipine effects were mediated at least in part via inhibition of CACNA1C. The functional significance of CACNA1C for the  $\text{Ca}^{2+}$  signaling of both glioblastoma cell lines can be deduced from the decline in resting  $\text{Ca}^{2+}$  concentration (i.e., control  $_{\text{free}}[\text{Ca}^{2+}]_i$ , see Figure 5E) upon knockdown of CACNA1C.

The notion of a presumable general anti-neoplastic function of benidipine in glioblastoma in concert with the observed TTFields stimulation of a benidipine-sensitive target that probably counteract the TTFields effects (at least in the TTFields more responding glioblastoma cell line T98G) provides a rationale to combine alternating electric field therapy with  $\text{Ca}^{2+}$  antagonists even in tumors with unknown TTFields responsiveness. Benidipine, which is in clinical use in Japan and India (Coniel®; Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan [59]) as anti-hypertensive drug is well tolerated. Tissue distribution in rats of orally applied benidipine indicates drug accumulation predominantly in digestive organs, mesenteric lymph nodes, liver, pancreas, urinary bladder, fat tissue, kidney and spleen [60]. The usually high penetrability of the glioblastoma blood barrier is expected to facilitate delivery of benidipine specifically to the glioblastoma while the blood brain barrier can be assumed to hamper distribution of benidipine in healthy brain parenchyma. Combined, this suggests that targeting of glioblastoma  $\text{Ca}^{2+}$  channels by benidipine or other FDA-approved  $\text{Ca}^{2+}$ -antagonists such as nifedipine [61] seems to be clinically feasible.

## 5. Conclusions

TTFields act on several molecular targets/pathways thereby influencing  $\text{Ca}^{2+}$ - and electrosignaling, cell cycle progression, programmed cell death, and clonogenic survival of glioblastoma cells. Concerning the most relevant parameter in oncology that is the clonogenic survival, TTFields responsiveness differed markedly between the two human glioblastoma lines tested suggesting that also in the clinical situation the benefit of TTFields therapy may vary considerably between individual glioblastoma patients. Knowledge of the underlying molecular mechanisms might be used for therapy stratification in the future or for pharmacological intervention and improvement of the tumoricidal TTFields effects. One such potential approach evolves from the present study that disclosed that  $\text{Ca}_v$  channel activity contributes to cellular stress response to TTFields and  $\text{Ca}_v$  inhibition may augment the TTFields effects.

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# Acceptance and compliance of TTFields treatment among high grade glioma patients

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## Abstract

**Background** Tumor treating fields (TTFields) significantly prolong both progression-free and overall survival in patients with newly diagnosed glioblastoma (GBM). TTFields are delivered to the brain tumor via skin transducer arrays and should be applied for a minimum of 18 h per day ( $\geq 75\%$  compliance). This may cause limited acceptance by patients because of obstacles in daily routine. So far, there are limited data on factors influencing therapy acceptance and compliance.

**Methods** In this retrospective study, forty-one patients with primary GBM or recurrent high grade glioma (rHGG) have been treated with TTFields in our department. Compliance reports were generated at the monthly routine check of the device. We investigated demographic data, stage of disease and therapy duration in regard to treatment compliance.

**Results** Thirty percent of patients with primary diagnosis of GBM were informed about TTFields. Acceptance rate among these patients was 36%. In this study, TTFields were prescribed in newly diagnosed GBM patients (57%) and in rHGG. Mean treatment compliance was 87% in the total population independent of age, sex and stage of disease. Compliance was not negatively correlated with time on treatment.

**Conclusion** TTFields are effective in newly diagnosed GBM, therefore acceptance and compliance is important for GBM treatment. We experienced moderate acceptance rate for TTFields, which is influenced by factors such as social support, comorbidities and independence in daily life. Overall therapy compliance lies above 75% and is not influenced by age, sex, stage of disease or duration of therapy. Improved patient consultation strategies will increase acceptance and compliance for better outcome.

**Keywords** Glioblastoma · TTFields treatment · OPTUNE® · Acceptance · Compliance

## Introduction

Standard of care in glioblastoma (GBM) treatment modalities consist of microsurgical resection, radiotherapy and chemotherapy [1]. However, GBM carries a dismal prognosis despite maximum treatment. Recurrence therapy includes re-resection, re-irradiation and recurrence chemotherapy, e.g. temozolomide (TMZ) rechallenge, nitrosurea, bevacizumab [2]. New investigative therapies include immune therapies, e.g. vaccine therapy, oncolytic viruses, checkpoint inhibition etc. [3]. However, recurrence therapy

is less standardized and is often based on caregiver's own experience and beliefs.

One new approach to improve tumor control in GBM is tumor treating fields treatment (TTFields, OPTUNE®, Novocure Ltd.) [4]. Alternating electric fields of low intensity (1–3 V/cm) and intermediate frequency (200 kHz for GBM) are delivered to supratentorial regions of the brain. Four transducer arrays applied to the shaved scalp (two in antero–posterior and 2 in coronal axes) deliver TTFields that target dividing tumor cells, which lead to mitotic catastrophe, autophagy and tumor cell apoptosis [5].

TTFields were introduced as salvage therapy in recurrent GBM. In the EF-11 study therapy proved to be equally effective to best physicians choice chemotherapy when TTFields were used as a monotherapy, despite not improving overall survival. EF-14 study showed that TTFields in patients with newly diagnosed GBM significantly prolonged both progression-free survival and overall survival (OS) by 2.7 and

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4.9 months, respectively [6], the use of TTFields is viewed with controversy among the neuro-oncological community based on the need for patients to stay at least 75% of time on therapy. Factors to consider for patients when deciding for TTFields are: necessity of hair shaving, frequent array change every 3–4 days, weight of device and spare batteries, visibility of the arrays, increased sweat rate in warm air temperature, alarm tone of the device and orthopedic problems carrying the device. These factors have to be outweighed by gaining increased tumor control and might negatively influence acceptance and compliance towards TTFields. In fact, no systematic data about factors influencing therapy acceptance and compliance exist. With this study we aim to investigate the acceptance of TTFields among high-grade glioma patients and factors contributing to therapy compliance.

## Materials and methods

### Patient cohort

In this retrospective study, we have analyzed data from 175 patients, who have been operated on a primary GBM. Histological diagnosis was confirmed by a neuropathologist. Each patient was presented at consensus conference. 73% of newly diagnosed GBM patients received adjuvant treatment in our institution. Treatment algorithm for newly diagnosed GBM patients in our department is as follows: patients younger than 70 years and in good clinical condition (KPS 70% and better) will be considered for Stupp protocol. Elderly patients (older than 70 years) with KPS 70% and better will be informed about treatment options according to Nordic trial, Perry scheme or Methvsalem study (NOA-08) [7–10]. Elderly patients harboring MGMT promotor methylation were offered temozolomide monotherapy. Table 1 displays detailed patients' characteristics of all GBM patients treated between May 2015 and February 2017 in our institution (primary therapy and tumor recurrence patients). In the same time period all recurrence patients presenting in our neurosurgical outpatient clinic were also screened for possible additional TTFields.

In May 2015, our department became a certified center for TTFields. From that time point on we adopted inclusion and exclusion criteria of EF-14 trial (clinicaltrials.gov Identifier: NCT00916409) for primary GBM therapy [11]. The following patients were considered candidates for TTFields: 18–70 years of age, KPS  $\geq$  70, life expectancy at least 3 months, supra-tentorial tumor and existing social support, e.g. another person who was able and willing to help with hair shaving and frequent array change. Patients with comorbidities like dementia, severe cognitive dysfunction, depression and severe aphasia were not considered eligible for TTFields, because one has to

assume that the patients cannot adequately handle and communicate discomfort about the therapy or technical problems and side effects.

For GBM recurrence, the same criteria had to be met to be offered TTFields as an add-on treatment to recurrence chemotherapy. However, due to the low level of evidence for recurrence therapy and after the publication of the EF-14 data we later decided to offer TTFields almost exclusively for primary treatment.

Hospital charts, medical reports and protocols of consensus conference were screened to identify patients to whom and when TTFields were offered and to identify factors influencing therapy acceptance among patients. Therapy compliance of patients under TTFields was assessed with the monthly gathered electronic records of the device. Here the average daily usage is recorded and the overall compliance for the period is calculated.

### Algorithm for TTFields introduction to GBM patients

We informed GBM patients in our neurosurgical department in a staged approach about TTFields. In case of initial diagnosis of GBM, the malignant diagnosis was communicated to the patient after surgery when we received histopathological diagnosis. As a first step, we explained the malignant nature of the disease and the need for adjuvant treatment. Patients were then introduced to concomitant therapy in the setting of a neuro-oncological outpatient clinic run by neurosurgeons. Here, neurosurgeons informed patients about the possibility of an additional treatment with TTFields (2nd step). We demonstrated the OPTUNE® device and handed out information material provided by Novocure. At the next appointment we discussed questions and concerns regarding TTFields and provided our interpretation of Phase 3 study results (3rd step). Prior to the publication of interim survival data of the EF-14 trial, we informed patients about the potential benefit of adding TTFields to standard therapy according to the interim analysis results and that clinical trial options in our institution would not interfere with TTFields. At that time point, no clinical studies were offered that had TTFields as exclusion criteria. We repeatedly informed patients about the logistics of the therapy including size and weight of the device (1.3 kg), rate of array change, battery life expectancy and the need of a care-giver in the patients' family or social circle for help in applying the arrays (social support). We informed patients about an adjusting phase of up to 4 weeks when patient and caregivers get familiar with the everyday challenges of the therapy. We also prepared the patient in advance about possible obstacles, e.g. skin reactions, and handling of the medical device. In the setting of recurrent disease, we offered TTFields as an additional therapeutic modality after re-irradiation, re-resection or



**Table 1** Patients' characteristics of all GBM treated between May 2015 and February 2017

	Newly diagnosed GBM n = 175		Recurrent GBM n = 96	
	n	%	n	%
Cases presented in consensus conference	175	100	96	100
Sex				
Female	68	39	44	46
Male	107	61	52	54
Age				
> 70 years	64	37	25	26
< 69 years	111	63	71	74
IDH status				
IDH-wildtype	167	95	92	96
IDH-mutant	8	5	4	4
MGMT promotor status				
Methylated	78	45	34	35
Unmethylated	90	51	49	51
n.a	7	4	13	14
Tumor localization				
Supratentorial single lesion	166	95	91	95
Multilocular	41	5	5	5
Surgical treatment				
Biopsy	47	27	5	5
Partial resection	40	23	0	0
Gross total resection	88	50	91	95
1st line treatment				
Stupp	91	52	71	74
Nordic	33	19	11	11
Perry	2	1	0	0
mTMZ	2	1	0	0
None	32	18	14	15
n.k	15	9	0	0
Therapy at recurrence				
Yes	51	29	58	60
None	124	71	38	40
Treatment modalities at recurrence				
Re-resection	18	35	41	43
Re-RTX	8	16	8	8
CCNU	5	1	11	11
mTMZ	24	47	41	43
BEV	8	16	20	21
Others	9	18	21	22
Follow up				
Mean (years)	0.62 (0–2.7)		1.23 (0–3.89)	

BEV bevacizumab, CCNU lomustine, GBM glioblastoma multiforme, IDH isocitrate dehydrogenase, KPS Karnofsky Performance Score, MGMT O<sup>6</sup>-methylguanine–DNA methyltransferase, mTMZ metronomic Temozolomide, na not assessed, nk not known, Nordic 40 Gy radiotherapy or six cycles adjuvant TMZ, Perry 40 Gy radiotherapy with concomitant TMZ and six cycles adjuvant TMZ, RTX radiotherapy, Stupp 60 Gy radiotherapy with concomitant TMZ and six cycles adjuvant TMZ, TTFields tumor treating fields

concurrent to chemotherapy re-challenge. During a period of 20 months, 41 patients decided and started TTFields at different stages of disease.

Once a patient opted for TTFields, they were then introduced by device support specialists to the logistics of therapy at home. NovoTAL (Novocure, Isreal) software was used



to calculate array placement based on the recent MRI [12]. Only patients who had supratentorial lesions were included in our study. The device support specialists generated compliance reports at least monthly and returned these to the prescribing physician. Compliance reports contain data about the average daily usage of the device and the overall compliance for the treatment period. MRI scans were done every 3 months to assess RANO criteria [13]. Patients gave their written informed consent to therapy. Ethics committee approval was obtained for publication of these data.

## Statistics

Statistical analysis was performed using GraphPad Prism 5 (GraphPad Software, La Jolla, CA, USA) and SPSS. Therapy compliance was measured as time on treatment per day and given in percent  $\pm$  standard deviation. 95% confidence interval (95% CI) were given, significance level was set at  $p < 0.05$ . Correlation tests were calculated with the Pearson test. Independent measures of two groups were performed with the Student's *t* test (therapy compliance, gender and stage of disease), independent measures of more than two groups with one-way ANOVA Bonferroni multicomparison test (therapy compliance, KPS and age groups). For non-parametric data, summary data was given as means, median and range.

## Results

### Characteristics of patients receiving TTFields treatment

Between June 2015 and February 2017, 41 patients accepted and started TTFields. Of these, 21 patients (54%) received primary therapy for GBM, 19 patients (46%) had recurrent disease, one patient harbored optic pathway glioma that was not classified as GBM. Fourteen patients were in first recurrence, three patients in second and two in third recurrence. The gender distribution among TTFields users was 16 females to 25 males (1:1.56). Mean age was 47.9 years (median 51 years, range 25–70). Mean KPS at therapy start was 83% (median 80%, range 50–100%) in newly diagnosed GBM and 78% in recurrent GBM (median 80%, range 60–100%). In seven patients KPS at therapy start was not assessed. Twenty-nine patients had IDH-wildtype glioma, seven tumors showed an IDH-mutation, and in five patients IDH-status was unknown. Fourteen patients showed methylation of the MGMT-promotor, while 22 tumors were unmethylated. Four tumors had unknown promotor methylation status. Detailed patients characteristics are shown in Table 2.

**Table 2** Data of patients receiving TTFields in newly diagnosed or recurrent GBM

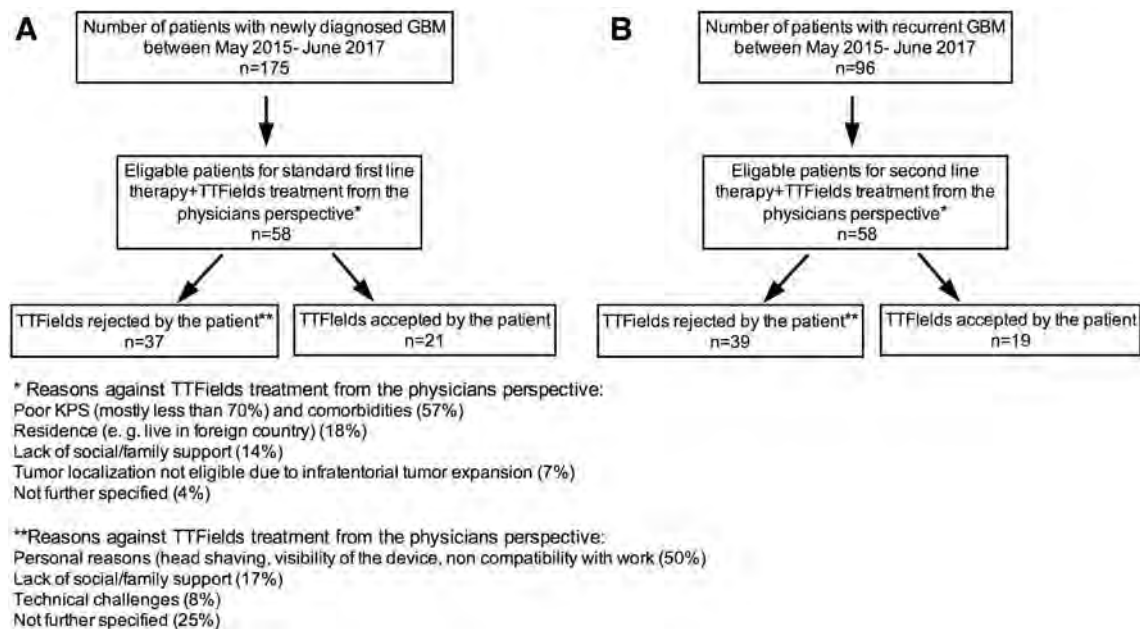
TTFields	Newly diagnosed GBM n = 21		Recurrent GBM n = 19	
	n	%	n	%
Sex				
Female	16	76	8	42
Male	5	24	11	58
Age				
> 70 years	1	5	0	0
< 70 years	20	95	19	100
KPS in%				
Mean	83		78	
Median	80		80	
Range	70–100		50–100	
IDH status				
IDH-mutant	3	14	4	21
IDH-wildtype	18	86	15	79
MGMT promotor status				
Methylated	5	24	9	47
Unmethylated	14	66	8	42
n.a	2	10	2	11
TTFields in addition to				
1st line therapy	21	100	–	–
2nd line therapy	–	–	14	74
3rd line therapy	–	–	3	16
4th line therapy	–	–	2	10
Prescription received from				
Neurosurgeon	21	100	19	100
Neuro-oncologist	0	0	0	0
Radiotherapist	0	0	0	0
Time on treatment in month				
Mean	6		4	
Median	5		2	
Range	(1–14)		(1–13)	
Compliance in %				
Mean	86		86	
Median	87		86	
Range	40–97		65–98	

GBM glioblastoma multiforme, IDH Isocitrate dehydrogenase KPS Karnofsky Performance Score, MGMT O<sup>6</sup>-methylguanine–DNA methyltransferase, TTFields tumor treating fields. Note that n=40 because one patient did not have diagnosis of GBM in the treated group

### Acceptance of TTFields parallel to first line therapy in GBM patients

TTFields were discussed as an additional therapeutic modality in combination to first line therapy in 58 (33%) out of 175 patients with initial diagnosis of a GBM (Fig. 1). Physicians decided against TTFields based on the





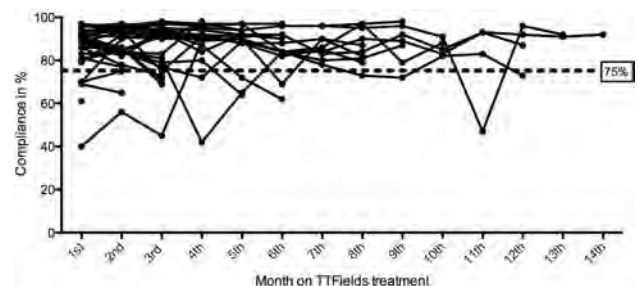
**Fig. 1** Number of TTFields considerations, rejections and assignments among patients with newly diagnosed glioblastoma (GBM) (a) and recurrent GBM (b)

following criteria: age > 70 years, not eligible for standard first line therapy (Stupp treatment), poor KPS (mostly less than 70%) and confounding comorbidities (mental disability including disorientation, dementia, severe memory problems, severe sensory aphasia, depression, neurological deficits like hemiparesis higher than grade 3 and if patients were non-ambulatory) in 57%, residence (e.g. residence in foreign country that kept patients from picking up disposable materials for TTFields) in 18%, lack of social/family support (14%), tumor localization not eligible due to infratentorial tumor expansion (7%).

TTFields were introduced to 58 patients with a new diagnosis of GBM according to the displayed algorithm. Of these, 37 patients decided against TTFields in addition to standard first line therapy, and 21 patients agreed to and started TTFields. Patients' arguments against TTFields were personal: head shaving, visibility of the device, impairment of mobility, independence in daily life, non-compatibility with work (50%), lack of social/family support (17%), technical challenges (8%) and unknown (25%). TTFields was offered to recurrence patients in good clinical condition who actively asked for therapy or inquired about therapies aside from a classical recurrence pattern of therapy only. These patients were mostly younger patients who wanted to do "everything possible" to prolong survival. 58 of 96 recurrence patients were classified eligible for TTFields (60.4%), in these patients acceptance rate was 19 out of 58 patients (32.8%). Overall, 19/96 patients received TTFields in the recurrence situation (19.8%).

### Therapy compliance in patients with newly diagnosed and recurrent GBM

Mean treatment duration was  $5.4 \pm 3.6$  months in all patients (7.2 months in primary therapy versus 4.3 months in recurrent disease). Treatment duration is not reflecting survival rates or progression-free time. Break or termination of TTFields was related to tumor progression followed by re-irradiation or re-resection or worsening of KPS etc. The efficacy of TTFields is optimal at treatment duration of more than 18 h per day, which corresponds to 75% or above compliance over treatment time. Among the investigated patients, the mean compliance was 86% per month (median 90, range 40–98%, Fig. 2). Only four patients stayed below the recommended 75% threshold on therapy within the first month under TTFields. Of these patients, two aborted therapy due to side effects (n = 1 worsening of pre-existing



**Fig. 2** Compliance data of all 41 patients in percent over time. Dotted line indicates the cut-off of 75% compliance



psoriasis and  $n=1$  because of anxiety episodes during treatment). The other two patients eventually exceeded the 75% mark while maintaining therapy. Some patients dropped below the 75% mark due to progressive disease associated with clinical worsening or a temporary discontinuation of therapy due to skin rash. Other reasons to temporarily pause therapy for a few days were holidays or to have a “short mental break” from therapy to stay motivated.

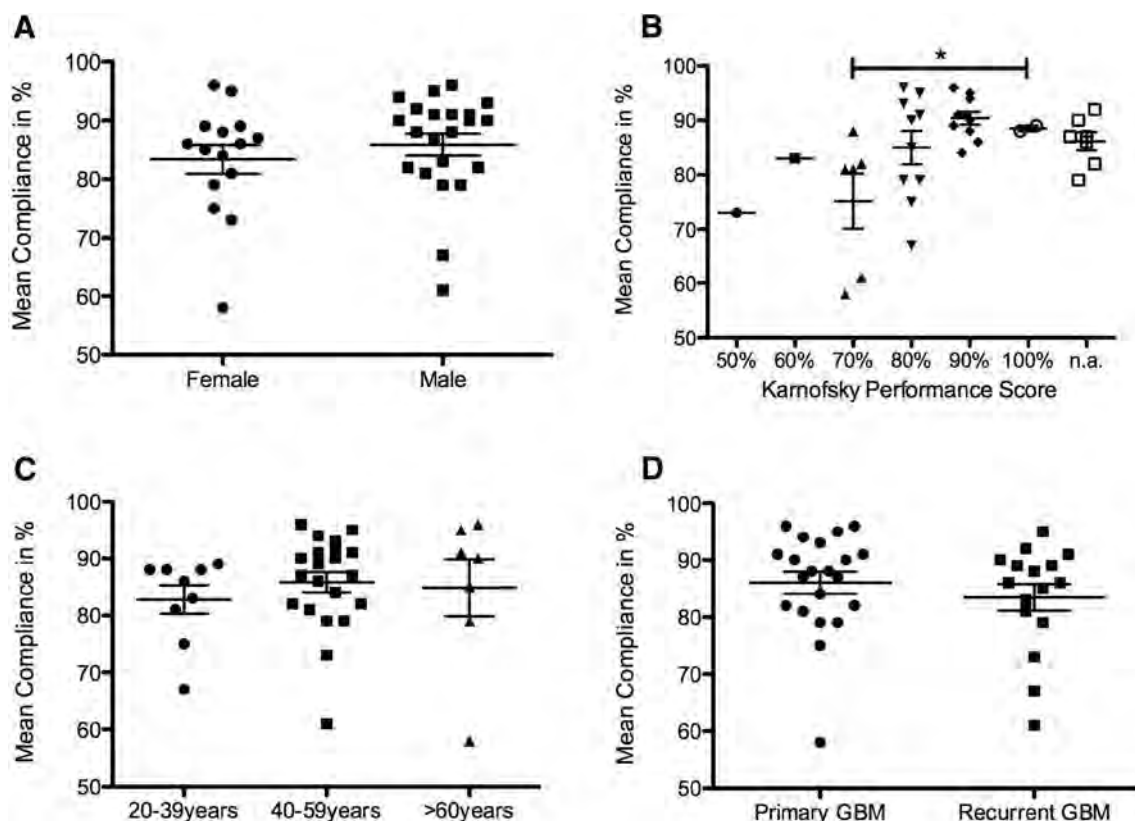
Overall, mean treatment compliance was  $84 \pm 2\%$  in female patients ( $n=15$ ) versus  $86 \pm 2\%$  in 22 male patients ( $p=0.410$ , Fig. 3a). A significant effect of KPS on compliance was seen only when comparing 70 versus 90% KPS ( $75 \pm 13\%$  vs.  $90 \pm 4\%$  [Mean  $\pm$  SD];  $p=0.017$ , Fig. 3b). However, patients in the 70% KPS group still managed to stay above 75% treatment compliance. Treatment compliance was compared among different age groups ranging from 20 to 39 years, 40–59 years and older than 59 years. No statistical difference between groups was found (Fig. 3c). Further, we assessed treatment compliance in regard to stage of disease. Mean compliance was 86% (median 87, range 40–97%) in newly diagnosed GBM versus 83% (median 86%, range 65–98%) in recurrent GBM (Fig. 3d,  $p=0.400$ ). Neither sex, age, KPS, nor stage of disease had significant

influence on treatment compliance. Our data showed that the compliance did not negatively correlate with time on treatment and compliance even stabilized once therapy was established.

## Discussion

In this study we show that TTFields are well accepted by GBM patients who are considered eligible/appropriate by the prescribing physician. Once patients have decided to accept TTFields, compliance rates are high and compare favorably to the data of the EF-14 study [11]. Our study shows that the goal being on therapy for 75% of the time can be achieved independently of age, sex, stage of disease or therapy duration.

Our patient cohort displayed a relatively low median age. This reflects the fact that younger patients tend to search more for additional treatment modalities and are more open-minded to accept relatively “new” treatment concepts to prolong survival. The lower median age explains the higher than normal rate of IDH mutations.



**Fig. 3** **a** Mean treatment compliance of male and female patients who received TTFields. **b** Mean treatment compliance in dependence of Karnofsky Performance Score,  $*p=0.017$ . **c** Mean treatment compli-

ance in dependence of age and primary versus recurrent glioblastoma (GBM) diagnosis (**d**)



According to the EF-11 trial and PriDe registry, TTFields should be applied at least 75% of the time in order to be as efficient as possible [14–16]. The comparably high compliance towards TTFields in this cohort possibly rely on the careful patient education and the staged approach of introducing this new therapy to the patient. In our view, an open, fair and honest information provided to the patient is crucial for acceptance and compliance to therapy. We openly inform patients about the logistics of the therapy, side effects, and the need for an adjusting phase of up to 4 weeks for patient and caregivers to get familiar with the everyday challenges of the therapy. Offering solutions beforehand makes the occurrence of these events more easily tolerable for the patient. In our view this certainly contributed to high therapy compliance even when encountering problems because patients knew beforehand about possible obstacles and handled them with more ease.

Due to the retrospective study design, results need to be interpreted carefully. On the other hand, the systematic user records of the device guarantee high data quality interpreting therapy compliance. Records show therapy compliance seems to depend more on the overall clinical status than on age alone. Even patients at the age > 59 years showed a remarkable average compliance far above 80% of the time and should be considered for TTFields if in good clinical condition and willing to use TTFields. KPS score is not associated with a substantial drop of compliance when above 70%. And even with a KPS of 70% the compliance is in the efficient range > 75% (Fig. 3b). On the other hand, patients who are wheel chair bound due to hemiparesis and have a formal KPS of 60% with strong request for additional treatment to chemotherapy might handle the device properly as well. Hence, we recommend not withholding TTFields in these cases and instead having an open discussion about the possibility of TTFields considering social support, patient's wish, biological age, etc.

In this study we show that compliance is equal in female and male population. Female to male ratio was 1:1.56 thus reflecting a typical GBM patient population (1:1.64) [17]. Additionally, there is no significant difference of compliance between patients with newly diagnosed and recurrent GBM suggesting that the stage of the disease does not play a big role for the acceptance and feasibility of the treatment. Since TTFields take time to be fully effective, compliance should be maintained on a high level to stay effective [18, 19]. Fortunately, compliance did not correlate negatively with time on treatment. Once patients are on therapy they mainly kept stable compliance over time, making TTFields suitable for long-term therapy. A drop in KPS almost exclusively showed progressive disease and clinical worsening that eventually led to therapy discontinuation. Treatment duration was 7.2 months for patients, which is comparable to the experience from the EF-14 study [6].

The low acceptance rate might be explained by restrained offer to elderly patients (> 70 years) and disabled patients or those having a reduced clinical status. We further assume that barriers to physicians introducing TTFields are not only concerns about patient compliance, but much more so nihilism about efficacy despite clinical trial data. Another reason to withhold therapy could be reluctance to accept mechanism of action of the therapy that differs significantly from standard chemo- or radiotherapy induced cytotoxicity.

From the patient side, there are mostly personal reasons for rejecting TTFields. Only 58/175 patients (33%) were deemed eligible for therapy by prescribing physician providing a careful selection process before offering therapy. Of these 58 patients, 37 (64%) rejected therapy due to the above stated reasons despite being offered solutions to possibly rectify encountered problems. Acceptance rate was 36% (21/57 patients) in the preselected cohort. Recently published data show that acceptance of TTFields increased up to 68% in newly diagnosed GBM patients by a more patient-centered consultation strategy [20].

We conclude that since we have demonstrated efficient compliance independent of age, sex, KPS and stage of the disease, TTFields should not be withheld from patients with advanced age or other comorbidities. Further improvement of technology resulting in decreased device size and weight will potentially also lead to improved handling and quality of life [18, 21]. Long-term use does not seem to affect compliance and allows efficient treatment even when exceeding 1 year. Thus, these criteria are not restricting possible TTFields candidates. To further improve acceptance for TTFields it is necessary to systematically assess reasons for refusing TTFields and improve these factors [22].

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# Tumor treating fields: a new approach to glioblastoma therapy

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## Abstract

Glioblastoma is an aggressive brain malignancy with poor outcomes. Current standard of care involves surgery, radiotherapy and chemotherapy. Even with optimal treatment, 5-year survival rates are low. Many patients are unable to tolerate the considerable side effects that therapy involves and suffer from low quality of life. Anti-mitotic tumor treating fields have shown potential in treating glioblastoma with data suggesting that they prolong disease-free survival and overall survival. Novocure has marketed a device that generates these fields via externally placed electrodes. Incorporation of electric field therapy into GBM treatment has been somewhat slow, due to concerns about cost, practicality of its usage from a patient perspective, and hesitation of the medical and scientific community to embrace its unconventional mechanism. However, clinical trials have demonstrated this therapy has relatively minor side effects and high patient compliance. In this review, we explore the current state of this technology and discuss the benefits and limitations of tumor treating fields.

**Keywords** Tumor treating fields · Glioblastoma · Cancer · Minimally invasive

## Introduction

Glioblastoma (GBM), a primary brain malignancy that accounts for 17% of all primary brain tumors [1], carries a poor prognosis with a 27% 2-year survival rate [2] and a median survival of 10–11 months with standard treatment [3]. The impact of this disease has spurred considerable investigation into potential treatments, but only a few have been associated with improved survival [4–6]. Quality of life is also an important consideration as the neurologic decline associated with disease progression combined with the toxicity of experimental chemotherapies has increased the need for new treatments for GBM to strike a balance between efficacy and tolerability. In 2011 Novocure's Optune Device, a novel therapy which applies alternating electrical fields or tumor treating fields (TTFs) to damage rapidly dividing tumor cells [7], was given FDA approval for treatment of recurrent GBM, with the approval expanded in 2015 to

include newly diagnosed GBM. Despite these approvals, incorporation of TTFs into GBM treatment has been somewhat slow, due to concerns about its cost, practicality of its usage from a patient perspective, and some slowness of the medical and scientific community to embrace its unconventional mechanism. In this article we will review the theory behind TTFs for cancer treatment. We will discuss recent clinical trials involving TTFs and the likely impact this technology will have in GBM treatment.

## Current standard of care

Glioblastoma has proven exceptionally resilient to treatment. Conventional treatment can typically be lumped into one of three categories: surgery, radiotherapy and chemotherapy [8, 9]. The first major tenant of GBM therapy is surgical resection. This has been shown to increase quality of life as well as prolong survival [8–10]. It has additionally been shown that extent of resection is a predictor of overall survival, with more extensive removal correlating with improved survival [11]. However, resection is not a curative approach [11, 12]. Therefore, providers often seek to augment the benefits of resection with radiotherapy and chemotherapy. The benefits of radiation therapy and TMZ after surgery have been well elucidated in the European Organization for

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Research and Treatment of Cancer (EORTC) Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada (NCIC) prospective study. This study determined that 27.2% (95% CI 22.2–32.5) of patients treated with both radiation therapy and chemotherapy survived to at least two years, compared to 10.9% (95% CI 7.6–14.8) with radiation therapy alone [13]. Alternatively, for patients that are not able to tolerate surgery or chemotherapy, radiation therapy is able to improve quality of life and increase survival alone [14]. Therefore, variants of surgery, radiotherapy, and chemotherapy have become staples of GBM treatment, but there is significant room for improvement. This is especially true for elderly patients, who may not be able to endure the significant burden of full-course chemotherapy and/or surgical resection [15].

### Preclinical study of electrical fields in cancer suppression

In addition to the approaches described above, the use of electric fields for cancer therapy has received great enthusiasm, if not a modicum of controversy about cost and efficacy. The Optune device is the best example of this technology and uses low intensity, intermediate frequency alternating fields to suppress cancer growth [16–18]. The Optune technology represents a prime example of bench-to-bedside translational medicine.

Electric fields have played a significant role in biology for many decades. Electroporation, the application of high intensity, high frequency electrical fields to facilitate cellular DNA transfer, is an essential technique of modern genetic experiments [19]. Similarly, intermediate intensity fields have been shown to cause cellular rotation and microscopic molecular alignment [20]. These phenomena are observed because many cellular substructures are composed of charged elements and thus are subject to electrical forces when an electric field is present [19–22]. Alternatively, as is the case with electroporation, minute differences in membrane potential (transmembrane voltage) in the presence of an electric field can reorganize membrane structure to create apertures [19]. In addition to applications in the basic sciences, electric fields have numerous clinical applications. For example, high frequency electric fields cause tissue dielectric energy loss and subsequent radioablation of nearby structures [23]. On the other end of the spectrum, low frequency electric fields have the capability of depolarizing nearby tissue and have applications in nerve conduction studies and cardioversion [24]. It was believed that intermediate frequency fields, which do not exhibit tissue heating or membrane depolarizing properties, would have limited clinical applications [19, 25].

In 2004 Kirson et al. demonstrated that very low intensity ( $<2$  V/cm) intermediate frequency (100–300 kHz) fields were capable of slowing tumor replication in vitro using cell culture and in vivo using mouse models [26]. The initial in vitro work demonstrated that multiple cell lines had impaired growth in the presence of the tested electric fields and that this effect persisted for at least 72 h after treatment. Follow-up microscopic analysis of cells treated with electric fields showed impaired depolymerization/repolymerization of the mitotic spindles and resulted in atypical mitoses and cell destruction. The authors also noted the significance of electric field orientation in respect to cellular layout—a point with significant clinical implication later. The work piloted by Kirson et al. has inspired a number of in vitro follow-up studies with intriguing results. Giladi et al. demonstrated that pancreatic tumors treated with TTFs increase in overall size, indicating both disruption of the mitotic cycle and possible dysregulation of cytoskeletal elements necessary for osmotic stasis [22]. More importantly, they were also able to show that TTF treated pancreatic cancer cells were less clonogenic than untreated controls. This reflected inability to generate new clonal lineages, likely due to aneuploidic divisions that were incompatible with further mitosis. These findings were further supported by the same authors in a paper the following year that concisely demonstrated the destructive effects of TTF on spindle apparatus formation by microtubule dysregulation [27]. Lastly, a study published this year identified that the mitotic dysregulation may make treated cells more susceptible to PARP inhibitors and ionizing radiation and suggests expanding the clinical role of TTFs [28].

The optimism generated from the in vitro work has inspired application of TTF into in vivo models. The seminal work by Kirson et al. contained the first application of TTFs to a living model and probed the possible use of this technology as a therapy [26]. These investigators, like many that followed, generated electric fields by surgically implanting wires into animal models—the technology to generate these fields less invasively came later. Using these fields, Kirson et al. showed an average 47% reduction in melanoma tumor size ( $p=0.001$ ) in mouse models. The application of these fields has been extended to other animal models and has shown efficacy in other tumor types, including lung, pancreatic and brain primary malignancy [22, 26–29]. In rabbits with melanoma metastases to the lungs, median survival was increased to 70 versus 57 days in controls [30]. This same work also demonstrated that treated rabbits and mice had fewer surface lung lesions and fewer large ( $>3.0$  mm) parenchymal lesions. While these teams were able to demonstrate efficacy in numerous animal models, the use of less conventional species has made replicating these findings more challenging. Follow-up studies in rabbits have been particularly limited despite being a foundational model for



this technology. Other investigators have shown that chemotherapy efficacy is potentiated in TTF treated animals [28, 31, 32]. This finding supports *in vitro* studies that proposed a synergistic effect of DNA damaging chemotherapeutics and TTF induced mitosis disruption. Additionally, the concept was extended to study intracranial tumors using externally placed electrodes [29]. This allowed multiple fields to be placed operating in three directions (0°, 45° and 90°) and showed a 53% reduction in tumor growth of intracranial GBM in mice ( $p=0.01$ ).

## Completed clinical trials

The work with *in vivo* models allowed TTF technology to mature into a clinically acceptable, minimally invasive tool for patient trials. Promising data in animal models engendered enough enthusiasm for a prospective clinical trial to test this therapy. Unfortunately, the results of the initial Phase 3 trial did not live up to the effect produced by pre-clinical study. This trial, EF-11 ( $n=120$  treated patients), was limited in scope and only applied TTF therapy in patients with recurrent GBM [33]. Patient populations suffered from significant heterogeneity, many were on their third recurrence and had failed chemotherapy numerous times. Additionally, the control arm was assigned to receive best physician-choice chemotherapy. TTF patients had a 6.6 month median survival, compared to 6.0 months in control arm ( $p=0.27$ ) and progression free survival of 2.2 months, compared to 2.1 months in controls ( $p=0.13$ ). However, side-effects from TTF were very modest and mostly consisted of skin irritation from the transducer pads [34]. The overall impression of this trial was two-fold: (1) In terms of survival and tumor progression, TTF therapy was not significantly worse than physician-choice chemotherapy for recurrent GBM and (2) TTF had a favorable side-effect profile and better overall quality of life than physician-choice chemotherapy.

While the first clinical trial suggested that TTFs were safe, there was still a need to test their effectiveness in patients with less advanced disease. In 2009 Novocure initiated a clinical trial to determine the impact of TTFs in conjunction with chemotherapy [35]. As described above, a number of preclinical studies had suggested that TTFs could potentiate the effects of chemotherapy. This trial, EF-14, involved patients with newly diagnosed glioblastoma who were treated with TTFs and temozolomide, or a control group treated with temozolomide alone. All patients had radiotherapy and TMZ before being randomized. The distribution of gross total and sub-total resection was comparable between the two cohorts. Initial analysis of this trial showed significantly improved progression-free survival (HR 0.62, 98.7% CI 0.43–0.89,

$p=0.001$ ) and significantly improved overall survival (HR 0.74, 95% CI 0.56–0.98,  $p=0.03$ ) in intention to treat analysis. Additionally, the patients randomized to TTF did not experience any significant toxicities and the treatment was well tolerated in the trial [36–38]. A final analysis of this study was released in December of 2017 and reported a median progression free survival (PFS) of 6.3 months in TTF treated patients, compared to 4 months in the control arm [39]. While this demonstrates that TTF treated patients had improved PFS, it is notable that the control PFS of 4 months is quite a bit lower than the 6.9 months of PFS reported in TMZ/radiotherapy treated patients in other studies [40, 41]. Lastly, the median survival of the TTF treated patients was 20.9 months, compared to the 16.0 months in the control group ( $p=0.001$ ). These findings have largely been corroborated by Mrugala et al. in their chart review of the Patient Registry Dataset (PRiDe) [42]. These authors reported markedly improved survival in patients with at least 75% daily compliance with the TTF protocol (HR 0.43,  $p=0.0001$ ). A notable limitation of both the EF-14 trial and the data from the PRiDe dataset is the lack of a true placebo control. EF-14, a randomized clinical trial, could have controlled for non-TTF treatment effect by applying a non-functional device to control patients. This additional measure could blind participants and providers more effectively and better determined the benefit of this device.

## Pending clinical studies

At the time of this report, there were 11 ongoing clinical trials for TTFs in GBM (Table 1). Although there has been demonstration of efficacy thus far, the exact role that TTFs should play in patient care is still evolving. Four of the current studies are assessing the role of the anti-angiogenesis agent bevacizumab, a monoclonal antibody against vascular endothelial growth factor A, as a supplement for TTF therapy [43, 44]. Although bevacizumab currently serves a limited role in current GBM management, it may have a synergistic effect when combined with TTFs [45]. One study is aiming to assess the effects of combined tumor-derived vaccine and TTF [46]. Another study is collecting specimens from deceased patients in the hope of identifying genetic changes that are induced with TTF therapy. It should lastly be noted that Novocure is assessing the application of TTF technology to other cancers, including lung, ovarian, pancreatic and mesothelioma malignancies. The data from these trials will likely inspire further work in glioblastoma and better define the role of TTFs.



**Table 1** Pending clinical trials

Trial name	Par- ticipant number	Study phase	NCT #	Study details
HUMC 1612: Optune NovoTTF-200A System	12	I	NCT03128047	Determine safety and tolerability of TTF in pediatric patients with high-grade glioma
NovoTTF Treatment Signatures in Glioblastoma Patients at Autopsy	20	–	NCT03194971	Identify tumor genetic signatures in patients treated with TTFs
Safety and Immunogenicity of Personalized Genomic Vaccine and Tumor Treating Fields (TTFs) to Treat Glioblastoma	20	I	NCT03223103	Test effects of personalized anti-tumor vaccine in combination with TTFs
NovoTTF Therapy in Treating Patients With Recurrent Glioblastoma Multiforme	30	II	NCT01954576	Measure effect of TTF therapy on recurrent GBM (Bevacizumab resistant and naïve)
Evaluating Therapeutic Response to Novo-TTF	30	–	NCT02441322	Determine if echo planar magnetic resonance spectroscopy (EPRS) is able to measure TTF effects on GBM
NovoTTF-200A and Temozolomide Chemoradiation for Newly Diagnosed Glioblastoma	10	I	NCT03232424	Safety and tolerability of TTF, TMZ and radiation therapy in combination. This study will involve brief application of TTF before radiosurgery and then reapplied after radiosurgery
A Phase II Study of Optune (NovoTTF) in Combination With Bevacizumab (BEV) and Temozolomide (TMZ) in Patients With Newly Diagnosed Unresectable Glioblastoma (GBM)	46	II	NCT02343549	TTFs will be applied after best standard of care radiation, temozolomide and bevacizumab
TTFs and Pulsed Bevacizumab for Recurrent Glioblastoma	25	II	NCT02663271	Continuous TTF therapy with repeat cycles of bevacizumab
Optune® Plus Bevacizumab in Bevacizumab-Refractory Recurrent Glioblastoma	85	II	NCT02743078	Will determine effect of TTFs and bevacizumab in tumors that failed to respond to bevacizumab alone
Enhancing Optune Therapy With Targeted Craniectomy	15	I	NCT02893137	Craniectomy (burr holes) will be placed for patients experiencing first recurrence to measure effects of TTF electrode placement
Optune(NOVOTTF-100A) + Bevacizumab + Hypofractionated Stereotactic Irradiation Bevacizumab-Naïve Recurrent Glioblastoma	27	–	NCT01925573	Determine safety and activity of TTFs, bevacizumab and hypofractionated radiosurgery in combination



## Limitations to date

As a novel technology, TTFs present a unique set of limitations to their use. In order to work effectively, the transducer pads must be applied directly to the skin [47]. Patients must shave their heads to allow the treatment pads to contact their scalp. The pads are applied with an adhesive and are usually changed every 3–4 days. While the pads are in place, patients must keep them dry, which can make bathing and recreational activities that involve water difficult. Once applied the device should be active 18 h a day to meet current recommendations. To make this possible, patients carry portable battery packs that supply energy to the transducers. Patients are free to travel, but must be able to change the batteries of their device every few hours. Each device comes with its own charging station and set of batteries. Therefore, patients must be willing to accept the limitations of the transducer pads, be willing to change batteries for the device every few hours, and keep their head shaved. Despite these requirements, compliance rates in the initial two studies exceeded 75% [33, 35]. The most significant side effects to therapy were skin irritation from the transducer adhesive or abrasion from the array pads. Although not trivial, these lesions typically responded to topical steroids and ultimately only 1–2% of patients had to discontinue therapy from these reactions. The risk of these lesions can be reduced by using gauze to protect areas that have a higher likelihood of irritation (incision scars, implanted devices, etc.) and training caregivers to care for the device and scalp [15, 48]. The larger limitation appears to come from patients unwilling to start this therapy due to perceived inconvenience of wearing the device. Although the initial clinical trials have reported good patient compliance, this may be biased by the relatively high enthusiasm of patients willing to participate in clinical trials.

Cost has been a concern about TTFs. While many patients have been able to access this technology through clinical trials, the Optune device, like many new therapies, comes at a considerable expense. It is estimated that each additional month of life attributable to Optune costs \$21,000 [49]. Even if the efficacy of TTF technology is validated, it may be prohibitively expensive and fail to reach widespread use. Despite enthusiasm from providers and patients alike, healthcare is a limited resource and can be sapped from the costs of cancer therapy [49, 50].

## Further areas of interest

As is mentioned in the review of the preclinical literature, TTFs may alter the genetic signature of treated tumors and make them susceptible to particular chemotherapeutic

agents [7, 16–18, 51, 52]. This could potentially make glioblastoma more susceptible to mitosis inhibitors or, as discussed above, expand the application of bevacizumab in therapy. Similarly, there is preclinical data that suggests TTFs can increase the anti-tumoral effects of ionizing radiation [53, 54]. Currently TTFs are applied after patients have undergone radiation therapy, but it is possible that a brief course of TTFs should precede radiation therapy for optimum effect. Lastly, there is some early work demonstrating that TTFs may activate local immune responses and could therefore have interplay with immunotherapy in the future [55].

## Conclusion

Since their discovery in 2004, tumor treating fields have quickly advanced from the bench to the bedside. Data from randomized clinical trials has demonstrated that TTFs increase patient survival and can be readily combined with other therapies. Although this technology has been met with skepticism, rigorous clinical trials have proven that they are effective in improving survival. In predicting the future of TTFs, the efficacy of this technology against a disease with a markedly dim prognosis and its low toxicity must be weighed against considerations such as cost and patient convenience. However, the drawbacks are tempered by the fact that other glioblastoma therapies have considerable costs and burdens as well. These factors suggest that TTFs are poised to develop a meaningful market share in the treatment of newly diagnosed and recurrent GBM during the upcoming years. This is particularly true in older patients, who may be less bothered by the inconvenience, may not tolerate the side effects of more aggressive treatments, and carry an elevated disease burden. Therefore, this technology strikes a balance between efficacy and toxicity that is desirable for many patients and will likely have a growing role in glioblastoma management.

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## Compliance with ethical standards

**Conflict of interest** The authors declare no conflict of interest.

**Research involving human and animals participants** No experiments were performed on animal or human subjects by the authors.

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# Molecular Evolution of a Glioblastoma Controlled With Tumor Treating Fields and Concomitant Temozolomide

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Tumor Treating Field (TTFields) therapy has demonstrated efficacy in a Phase 3 study of newly diagnosed glioblastoma (GB) following radiation (RT) and temozolomide (TMZ). We report the appearance of an isolated satellite anterior temporal lobe lesion, 2 months post primary RT/TMZ directed at the primary GB (MGMT methylated) parietal lobe lesion and one adjuvant cycle of TMZ and TTFields. The mean RT dose delivered to the temporal lobe lesion was negligible, i.e.,  $4.53 \pm 0.95$  Gy. Mapping of the generated TTFields demonstrated that both lesions were encompassed by a field intensity in a therapeutic range. The temporal lobe lesion remained under the control of TTFields up to 12 months, at which point progression on a T1 contrast MRI resulted in surgery and a definitive diagnosis of GB without MGMT methylation. The primary parietal lobe at this time was in remission. Molecular sequencing on the GB tissue from multiple time points demonstrates clonal evolution of the cancer over time and in response to treatment.

**Keywords:** glioblastoma, tumor treating fields, optune®, genomics, temozolomide

## INTRODUCTION

Tumor Treating Field (TTFields) therapy has demonstrated efficacy in a Phase 3 study of newly diagnosed glioblastoma (GB) following radiation (RT) and temozolomide (TMZ) (1), as well as in the recurrent setting (2). Interestingly, there have been no reports of TTFields therapy in GB patients who have not received prior RT. In addition, the potential mechanisms by which resistance to TTFields therapy develops has been understudied.

In the report to follow, an analysis of a satellite lesion that developed after standard RT and TMZ therapy in a newly diagnosed GB patient is presented. Therapy with TTFields had been initiated 1 month prior to the appearance of the satellite lesion. The patient was followed longitudinally with MRIs every 2 months; additional analysis of the radiation dose exposure, as well as the TTFields intensity, was performed. The differential diagnosis at the time included an MRI artifact or lesion induced by TTFields, vs. progressive disease. After 12 months, the aforementioned lesion



was resected. Molecular alterations from baseline, post-progression on TTFields and following a further recurrence were assayed. The results below summarize these collective findings.

## CLINICAL DETAILS AND DATA ANALYSIS

In March 2016, a 51-year old male presented with left-sided numbness and weakness. A MRI demonstrated a  $35 \times 25 \times 29$  mm partially cystic or necrotic, enhancing mass with internal hemorrhage in the right parietal lobe. Subtotal resection was accomplished in March 2016 confirming a grade 4 astrocytoma with IDH1/2 wild type, MGMT methylated, and negative 1p19q co-deletion.

Standard radio-chemotherapy was completed in June 2016 (3), including daily TMZ with a total of 60 Gy radiation give in 30 fractions; adjuvant TMZ began in July 2016. TTFields therapy (1) was initiated in July 2016 and continued until August 2017. A post-radiation MRI was done in August 2016, showing increased thickness of the residual enhancing region in the right parietal lobe in addition to a new lesion in the right middle temporal gyrus (Figure 1).

Changes of residual tumor in the right parietal lobe was presumed to be progression vs. pseudo-progression, and the patient continued with six cycles of adjuvant TMZ, which was completed in December 2016. The changes in the parietal lobe lesion resolved over time, confirming pseudo-progression. In spite of the appearance of the temporal lobe lesion, it was decided to continue therapy with both TMZ and TTFields (with frequent monitoring), as the possibility of an artifact of TTFields therapy and/or an unusual form pseudo-progression was raised.

On a series of follow-up MRIs from August 2016 to August 2017, the initial parietal lobe lesion regressed with adjuvant TMZ and appeared stable on both T1+contrast and T2/FLAIR MRIs. The new enhancing lesion in the temporal lobe (during adjuvant TTFields/TMZ therapy) decreased from 9 to 7.7 mm in diameter with decreasing enhancement from August 2016 to November 2016 (Figure 1), and stayed stable on bi-monthly follow up MRIs until August 2017. At this time the temporal lobe lesion was at 17.9 mm in diameter (on T1+contrast); the parietal lobe lesion was essentially resolved, confirming pseudo-progression of this tumor (Figure 1). T2/FLAIR images showed abnormality with an area of restricted diffusion and peripheral rim enhancement in the region of the right temporal lobe lesion. A gross total resection of the temporal lesion was achieved in August 2017, confirming a grade 4 astrocytoma, with wild type IDH1/2, unmethylated MGMT, and negative 1p19q co-deletion (Figure 2). The mean prior radiation dose for this temporal lesion was determined to be  $4.53 \text{ Gy} \pm 0.95 \text{ Gy}$  (5.7 Gy max; 3.5 Gy min; volume 0.1 mL). An isodose cloud is depicted (Figure 3). The lesion was 2.5 cm away from the edge of the planning target volume treated to full dose (46 Gy; center lesion dose 60 Gy).

The patient was then treated (September 2017–November 2017) with radiation (60 Gy in 30 fractions), targeting the temporal lobe resection cavity. An MRI in January 2018 demonstrated a possible new nodule ( $0.7 \times 0.7$  cm) on the edge

of the resection cavity. A subsequent MRI in February 2018 confirmed progression with an increase in the aforementioned nodule to  $1.4 \times 1.8$  cm. In March 2018, the patient underwent reoperation with a gross total resection as part of the TOCA 5 Tocagen Inc. clinical trial and was randomized to the control arm post-operatively. He started bevacizumab therapy in April 2018 which maintained his surgically obtained complete remission until relapse in August 2018.

Molecular analyses demonstrate that at resection of the primary parietal lobe lesion this cancer possessed mutations in *BRAF* (V600E), *PTEN* (319fs), and the *TERT* promoter (C228T). Following progression on TTFields, the separate anterior temporal lesion was resected. This lesion possessed these identical *BRAF*, *PTEN*, and *TERT* alterations, and was also found to possess a deep deletion of *CDK2NA* and an activating mutation in *mTOR* (V2006I). The lesion in the anterior temporal lobe that recurred following radiation was also sequenced following resection. This lesion was hypocellular, and similar to the prior resection exhibited mitosis, nuclear atypia and no necrosis; the same *BRAF*, *mTOR*, and *TERT* abnormalities were still able to be observed. No new alterations were detectable in this sample.

Additionally, a retrospective analysis demonstrated the TTFields intensity was in a therapeutic range for both the parietal lobe and temporal lobe lesion, i.e., 1 V/cm (Figure 4).

## METHODS

### Bio-Marker Testing

MGMT testing performed by LabCorp, NC; IDH testing done by PCR, UW Health Clinical labs, WI, 1p19q testing by FISH, Wisconsin State Laboratory of Hygiene.

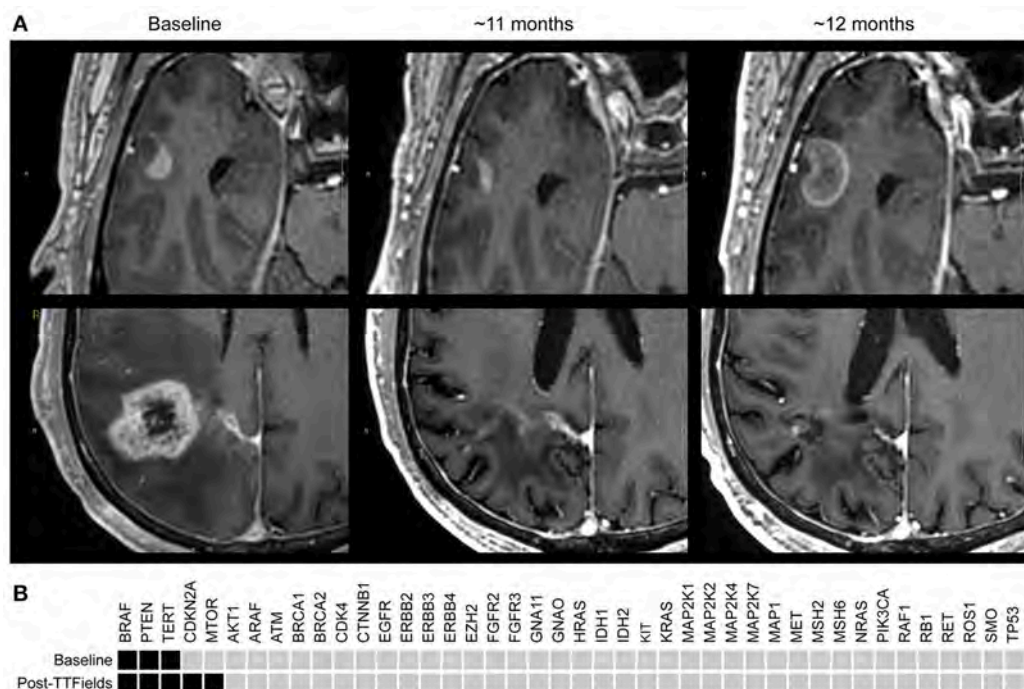
### Determination of Radiation Dose

Using image registration software (Mim Vistag Cleveland, OH) that imports the radiation dose, the axial contrast-enhanced 3D T1-weighted images (T1 3D-SPGR Bravo, GE Healthcare, Waukesha, WI) were fused into a coordinate system of the treatment planning CT. A region of interest was drawn around the anterior temporal lobe lesion, and dosimetric analysis revealed the prior RT dose to the lesion.

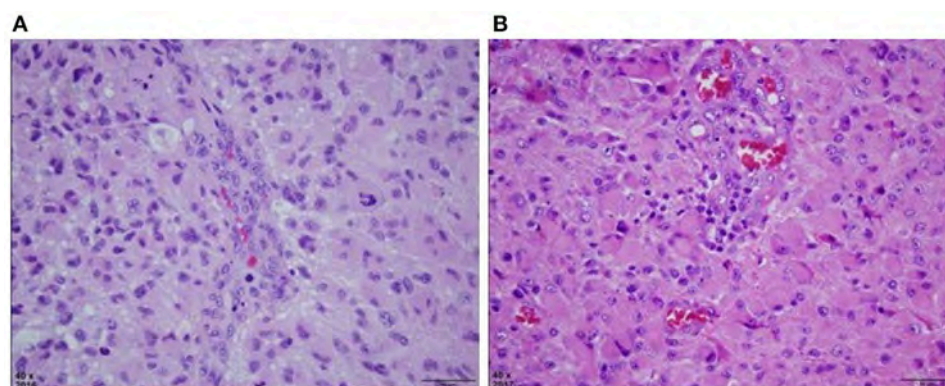
### Mapping of TTFields Intensity

In order to estimate field intensity distributions within the lesions, numerical simulations were performed using finite differences Time Domain (FDTD) calculations and a realistic head model as described in Wenger et al. (4). Briefly, a realistic head computational model of a healthy male was created and scaled to match the dimensions the patient's head. Transducer arrays for the delivery of TTFields were positioned on the head model to mimic the personalized transducer array layout that was placed on the patient. In order to establish whether or not TTFields were delivered at therapeutic levels to the tumors, ellipsoidal regions approximately encompassing the lesions were manually marked on the field intensity maps. The field was considered to deliver TTFields at therapeutic levels to the lesion if the median field intensity within the respective ellipsoid exceeded 1 V/cm (5).





**FIGURE 1 | (A)** T1+contrast MRI images: Upper panels are right temporal lobe; lower panels are corresponding right parietal images. *Baseline* (Aug. 2016) demonstrates the first appearance a temporal lobe lesion ~2 months post radiation/temozolomide; the lower panel demonstrates the primary GB. Middle section ~11 months later (June 2017) demonstrates slightly less enhancement of the temporal lobe lesion, and a dramatic reduction in enhancement and size of the parietal lobe lesion with decreased edema and treatment related cerebral atrophy. At ~12 months (Aug. 2017) the temporal lobe lesion has increased to 18 × 13 mm; the parietal lobe remains stable and in remission. **(B)** StrataNGS cancer hotspot sequencing was performed on the resection of the primary parietal lobe lesion, which possessed mutations in *BRAF* (V600E), *PTEN* (319fs), and the *TERT* promoter (C228T). Following progression on TTFields, the separate anterior temporal lesion was resected and demonstrated *BRAF*, *PTEN*, and *TERT* alterations, and the acquisition of a deep deletion of *CDK2NA* and an activating mutation in *mTOR* (V2006I). No other pathologic alterations were identified in the remaining 47 genes of the 88 genes assessed.



**FIGURE 2 | (A)** H&E stained section of right parietal tumor at original magnification of 40x, reveals a densely cellular astrocytic neoplasm with nuclear atypia, mitosis, and vascular endothelial proliferation. Palisaded necrosis was also present but not shown in this field. **(B)** H&E stained section of right temporal mass at original magnification of 40x, also reveals a densely cellular astrocytic neoplasm with slightly more gemistocytic features, nuclear atypia, mitosis, and vascular endothelial proliferation that was similar to the previously resected tumor. This material lacked necrosis.

## Strata Oncology Hot Spot Sequencing

Patient samples were sequenced through STRATA Oncology CLIA-certified laboratory using the StrataNGS platform. This panel covers 88 genes and examines predefined variants

including single and multinucleotide alterations, small insertions/deletions, fusions, exon skipping mutations, copy number variation, and microsatellite instability ([www.strataoncology.com](http://www.strataoncology.com)).



## DISCUSSION

In this report, we present the first instance of a grade 4 astrocytoma controlled by systemic TMZ and TTFields, with negligible radiation exposure. The patient's initial parietal lobe lesion was MGMT methylated, not IDH mutated, and not 1p19q deleted; the resected temporal lobe lesion was similar histologically, but was not MGMT methylated. Based on the

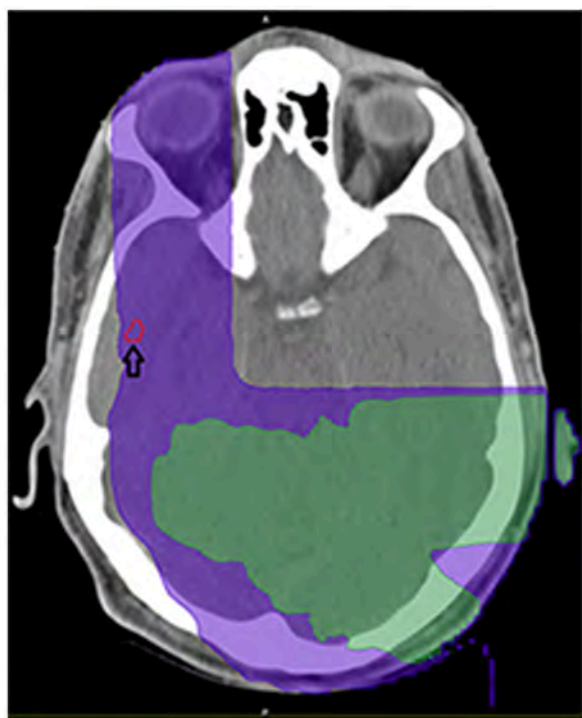
MRIs between June 28th to August 14th, 2016 (**Figure 1**), the volume doubling time was calculated (6) as 14 days for the temporal tumor.

As the temporal lobe tumor appeared after initial concurrent radiation and TMZ treatment, this tumor may have been TMZ resistant, which is consistent with the absence of methylation on MGMT promoter. Alternatively, a resistant TMZ clone may have evolved over time. The initial radiation field was reconstructed, showing that the temporal lobe was exposed to minimal radiation at the time,  $4.53 \pm 0.95$  Gy. This region, however, was within the TTFields effective region, suggesting that the suppression of tumor growth from August 2016 to 2017 was under the control of adjuvant TMZ and/or TTFields.

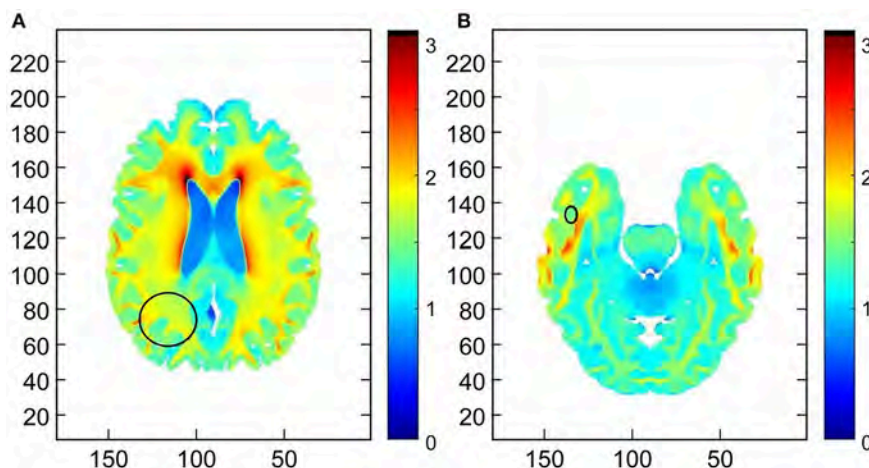
The original plan for the placement of Optune™ arrays using the NovoTAL™ methodology (7) targeted the right parietal lesion. It was not intuitively obvious that the field distribution in the temporal lobe region would be sufficiently high to have a therapeutic effect. Hence, numerical simulations (**Figure 4**) were performed; the simulations demonstrate that the field intensity delivered to both lesions was at therapeutic levels ( $>1$  V/cm). Taken collectively, these data support the efficacy of TTFields in a newly diagnosed GB regarding a lesion that received a negligible dose of ionizing radiation. The contribution of adjuvant TMZ in controlling this lesion is indeterminate as discussed above.

Based on the molecular sequencing we can see that the cells within the anterior temporal lobe lesion developed from cells in the original primary parietal lobe lesions as the exact alterations were identified in both instances. The additional alterations identified presumably arose through clonal selection. While many factors could have potentially played into this selection process, we propose that it is quite plausible that the activating mutation in mTOR and/or the deep loss of CDKN2A could be inducing the resistance to TTFields therapy.

Over the last few years, new mechanistic insights have been gained into the anti-cancer effects of TTFields. These potential mechanisms of action include disruption of key



**FIGURE 3 |** Demonstration of isodose cloud for temporal lobe lesion (see arrow). Purple denotes 5Gy isodose; green denotes 8.57 Gy isodose.



**FIGURE 4 |** Demonstration of the field intensity distribution in axial slices through the centers of the (A) primary right parietal lobe lesion and (B) the right temporal lobe secondary lesion. The median field intensity in the region of the primary lesion was 1.7 V/cm (mean of 1.66 V/cm). In the region of the secondary lesion the median intensity was 1.48 V/cm (mean of 1.56 V/cm). This suggests that TTFields intensities around both lesions exceeded the therapeutic threshold of 1 V/cm.



cellular functions, such as mitosis, DNA repair, mitochondrial function, and the folded protein response, leading to the induction of cellular stress, autophagy and apoptosis (5, 8–10). TTFields has also been implicated in enhancing the immune response through the induction of immunogenic cell death and modulation of antigen presentation (11). Loss of CDKN2A could lead to cell cycle dysregulation and mTOR activation could lead to inhibition of autophagy, apoptosis, and enhance cell proliferation overcoming some of the potential mediators of response to TTFields (12, 13). In addition, activation of the PI3K/AKT/mTOR signaling pathway has been associated with immune suppressive properties, including the up-regulation of the PD-L1 immune checkpoint.

In summary, this report provides evidence that TTFields may offer prolonged therapeutic benefit for some patients with recurrent GB. The molecular analysis of this patient's cancer over time provides potential insight to mechanisms by which resistance to TTFields might occur. This work also raises several interesting questions about how clonal evolution and spread through the central nervous system occurs, whether targeting therapies, such as mTOR or BRAF inhibitors, could be used in settings like this, and whether more routine molecular profiling should be obtained for patients with GB. Clearly, as we learn more about the biology of individual patients with GB this will lend itself to more precision-based treatment strategies for patients.

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## ETHICS STATEMENT

This is a case report regarding a patient treated with FDA approved standard of care treatment. Informed consent was obtained.

## AUTHOR CONTRIBUTIONS

HN contributed to the clinical history review, literature review, and manuscript preparation. SH evaluated radiation dosing and reviewed the manuscript. SS reviewed pathology. AF reviewed the manuscript and MRI scans. HR identified the patient, reviewed the clinical history and the literature, and prepared the manuscript. DD performed the genomic analyses and edited the manuscript.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ARTICLE

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# AMPK-dependent autophagy upregulation serves as a survival mechanism in response to Tumor Treating Fields (TTFields)

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## Abstract

Tumor Treating Fields (TTFields), an approved treatment modality for glioblastoma, are delivered via non-invasive application of low-intensity, intermediate-frequency, alternating electric fields. TTFields application leads to abnormal mitosis, aneuploidy, and increased cell granularity, which are often associated with enhancement of autophagy. In this work, we evaluated whether TTFields effected the regulation of autophagy in glioma cells. We found that autophagy is upregulated in glioma cells treated with TTFields as demonstrated by immunoblot analysis of the lipidated microtubule-associated protein light chain 3 (LC3-II). Fluorescence and transmission electron microscopy demonstrated the presence of LC3 puncta and typical autophagosome-like structures in TTFields-treated cells. Utilizing time-lapse microscopy, we found that the significant increase in the formation of LC3 puncta was specific to cells that divided during TTFields application. Evaluation of selected cell stress parameters revealed an increase in the expression of the endoplasmic reticulum (ER) stress marker GRP78 and decreased intracellular ATP levels, both of which are indicative of increased proteotoxic stress. Pathway analysis demonstrated that TTFields-induced upregulation of autophagy is dependent on AMP-activated protein kinase (AMPK) activation. Depletion of AMPK or autophagy-related protein 7 (ATG7) inhibited the upregulation of autophagy in response to TTFields, as well as sensitized cells to the treatment, suggesting that cancer cells utilize autophagy as a resistance mechanism to TTFields. Combining TTFields with the autophagy inhibitor chloroquine (CQ) resulted in a significant dose-dependent reduction in cell growth compared with either TTFields or CQ alone. These results suggest that dividing cells upregulate autophagy in response to aneuploidy and ER stress induced by TTFields, and that AMPK serves as a key regulator of this process.

## Introduction

Tumor Treating Fields (TTFields) are an established anti-mitotic treatment modality delivered via non-invasive application of low-intensity (1–3 V/cm), intermediate-frequency (100–300 kHz), alternating electric fields to the tumor region<sup>1–3</sup>. In a randomized phase 3 study (NCT00916409) TTFields in combination with

maintenance temozolomide significantly prolonged progression-free and overall survival of newly diagnosed glioblastoma patients when compared with patients receiving maintenance temozolomide alone<sup>4</sup>. Previous studies have demonstrated the effectiveness of TTFields application in various cancer cell lines, as well as in in-vivo models and in the clinical setting<sup>2,3,5–7</sup>. TTFields intrinsically affect molecules that possess high electric dipole moment and promote a number of anti-mitotic effects including the disruption of the spindle structure through microtubules depolymerization and perturbation of cytokinesis through mitotic Septin complex

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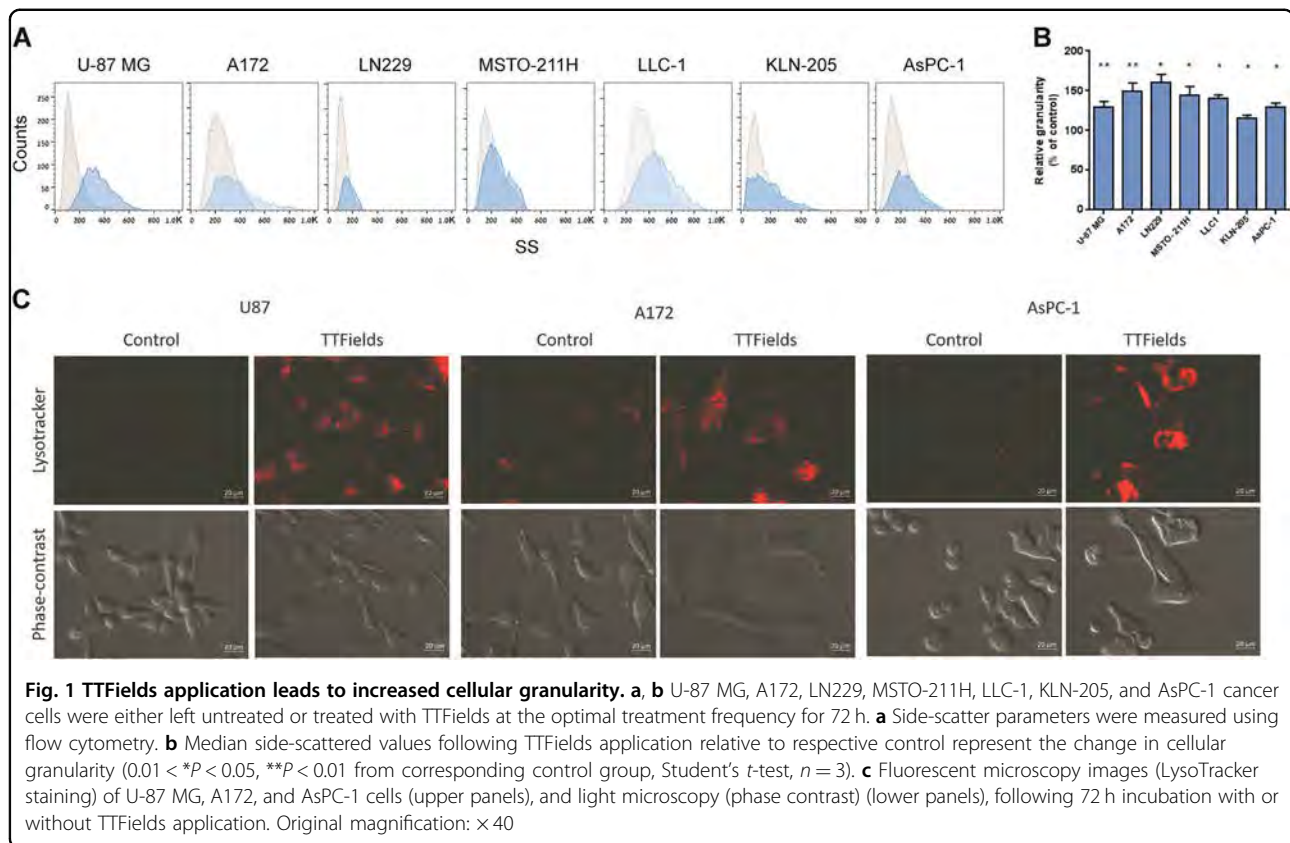
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mislocalization, both of which may ultimately lead to mitotic catastrophe<sup>3,8,9</sup>.

More recent studies have also revealed the inhibitory effects of TTFields on cell migration and invasion via downregulation of phosphoinositide 3-kinase (PI3K)/AKT/nuclear factor- $\kappa$ B signaling<sup>10</sup> and the capability of TTFields to sensitize cancer cells to radiation by impeding the DNA damage response, possibly through downregulation of the BRCA1 signaling pathway<sup>11–13</sup>.

Several studies have shown that cells treated with TTFields demonstrate an increase in cell volume and granularity<sup>9,14</sup>. Increased cellular granularity is typically associated with senescence and autophagy<sup>15,16</sup>. As senescence was not detected in cells treated with TTFields, we hypothesized that the origin of the observed granularity may be due to the accumulation of autophagosome vesicles<sup>8</sup>. A recent study supports this hypothesis by providing evidence that TTFields induce autophagy in glioma cell lines<sup>17</sup>. Observations that autophagy was stimulated under stress conditions and was shown to be involved in cell survival and proliferation have prompted interest in the relevance of autophagy in human disease, including cancer, and its role in treatment resistance<sup>18,19</sup>. The role of autophagy in cancer is complex<sup>20,21</sup>. Autophagy can have a tumor suppressive function at early stages of cancer development and promote tumor cell survival in

established tumors<sup>22</sup>. Autophagy also facilitates the resistance of tumor cells to anticancer agents<sup>23</sup> and to radiation<sup>24</sup>.

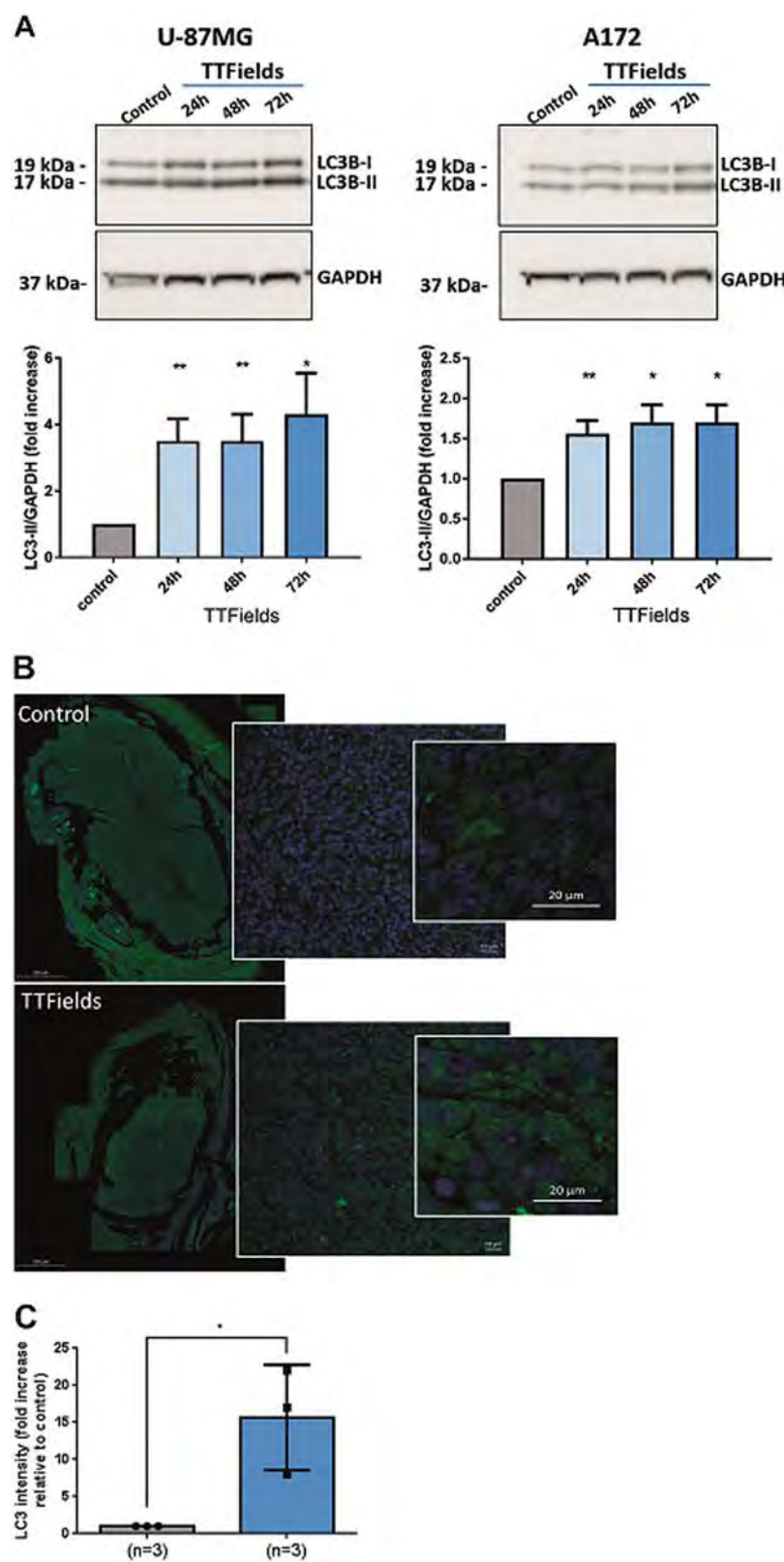
The objective of the current work was to understand the effects of TTFields on cancer cells in terms of autophagy. Specifically, we show that the abnormal mitosis induced by TTFields upregulate proteotoxic stress response leading to AMP-activated protein kinase (AMPK) activation and increased autophagic flux in treated cells. Our findings support that the enhanced autophagy serves as a resistant mechanism to TTFields, which could be circumvented by targeting autophagy.

## Results

### Effects of TTFields on cellular granularity

To establish whether changes in cell granularity are a common outcome of TTFields application, we used flow cytometry analysis of side-scatter parameters (i.e., granularity), in various cancer cell lines, including the following: mesothelioma (MSTO-211H), glioma (U-87 MG, A172, LN229), lung (LLC-1, KLN-205), and pancreatic (AsPC-1) cancer<sup>25</sup>. In all cell lines tested, TTFields application resulted in changes in cellular granularity (Fig. 1a, b)<sup>25</sup>. This can potentially be attributed to lysosomes accumulation, which was confirmed by fluorescent microscopy of LysoTracker-stained cells, which





**Fig. 2** (See legend on next page.)



(see figure on previous page)

**Fig. 2 TTFields induce autophagy in glioma cell lines.** **a** U-87 MG and A172 cells were either left untreated or treated with TTFields at the last 24 h, 48 h, or 72 h of culturing. All cultures were plated on the same time, incubated overnight to allow cell attachment, and collected 72 h afterwards. Cells were collected, lysed, and samples were analyzed using immunoblotting for LC3 and GAPDH. Upper panel: representative blots. Lower panel: densitometric quantification of immunoblot signal, showing an average of at least three independent experiments ( $0.01 < *P < 0.05$ ,  $**P < 0.01$ , Student's *t*-test). **b** Paraffin-embedded sections from sham- or TTFields-treated rats were stained with anti-LC3 Ab (green) and DAPI (blue). Representative images are presented. **c** Quantification of LC3 intensity, presented as fold increase from corresponding control ( $*P < 0.05$ , Student's *t*-test)

demonstrated larger acidic lysosomal pool in TTFields-treated cells (Fig. 1c).

### TTFields increase autophagosome formation and autophagic flux

To explore whether the appearance of the cellular lysosomes following TTFields application is attributed to autophagy, we used immunoblot assay to quantify light chain 3 (LC3) in U-87 MG and A172 glioma cell lines. LC3 is a cytoplasmic protein that on induction of autophagy is converted to LC3-II through lipidation, allowing its association to the autophagic vesicle membrane<sup>26</sup>. Immunoblot assay revealed that LC3-II signal increased after TTFields application, and that this increase in autophagosome formation was dependent on treatment duration (Fig. 2a). To test whether TTFields also increased autophagosomes formation *in vivo*, we treated Fisher rats inoculated intracranially with F98 glioma cells (as was previously reported by Kirson et al.<sup>2</sup>) with either TTFields or sham control, and stained the tumor sections for LC3. Application of TTFields was associated with noticeable increase in autophagy (Fig. 2b, c).

The accumulation of autophagosomes, as measured by LC3-II levels, may indicate sheer upregulation of autophagy or it may reflect reduced autophagosome turnover due to defects in autophagosome transport and autophagosome–lysosome fusion. Electron microscopy (EM) observation of ultra-structures revealed membrane-bound vesicles containing cytosolic materials or organelles, and the presence of degradative autophagic vacuoles containing partially degraded material, which was more abundant following TTFields application, indicating the existence of autophagic structures and an effective fusion process (Fig. 3a; blue and green arrows).

To further validate these observations, Chloroquine (CQ; a known inhibitor of lysosomal degradation) was added 3–4 h before treatment end. The addition of CQ, which prevents LC3-II degradation and release back to the cytoplasm, resulted in a significant increase in the LC3-II levels in cells treated with TTFields relative to control cells, as shown by immunoblotting (Fig. 3b, Supplementary Figure 1), immunofluorescent staining for quantification of LC3 puncta (Fig. 3c), as well as autophagic vacuoles accumulation using EM (supplementary figure 2).

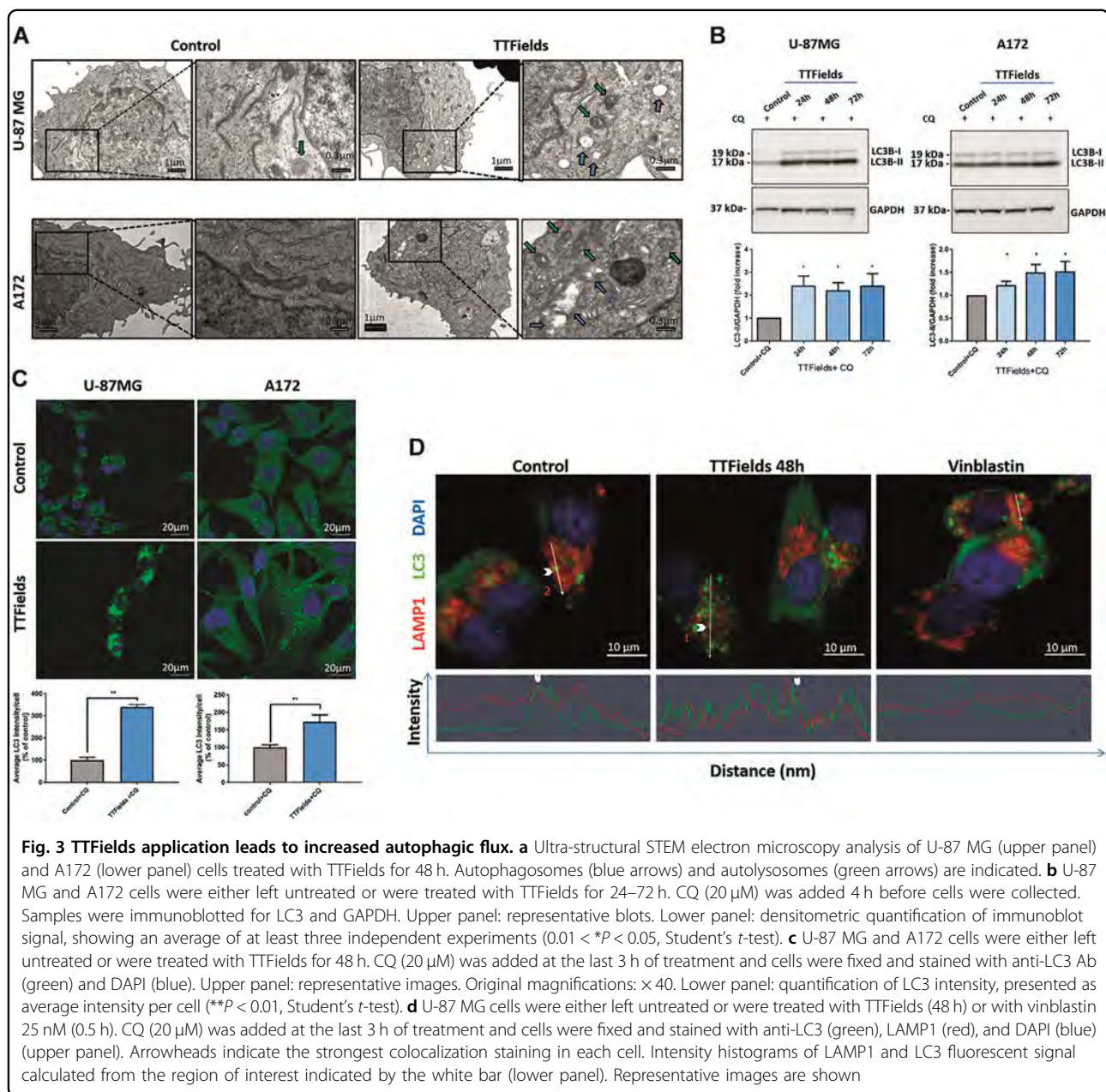
Direct evidence for normal autophagosome-to-lysosome fusion under TTFields application was obtained using immunofluorescent staining of LC3 foci with the lysosomal marker LAMP1. Unlike vinblastine, a known inhibitor of autophagosome trafficking, which led to dispersed localization of the two markers, TTFields application did not perturb LC3 and LAMP1 colocalization (Fig. 3d).

Taken together, these results demonstrate that TTFields application lead to an increase in the autophagic flux in glioma cell lines with no substantial influence on the fusion degradation steps.

### Stress response in daughter cells produced under TTFields application upregulate autophagy

Abnormal mitosis following TTFields application results in different cell fates including the formation of aneuploid daughter cells<sup>7,8</sup>. Aneuploidy is associated with the activation of regulators of autophagic and lysosomal gene expression<sup>27,28</sup>. To explore whether autophagy was more prominent in cells that divided during TTFields application, we analyzed autophagosome dynamics within single cells using U-87 MG cell line stably expressing LC3 protein fused with green fluorescent protein (GFP). We utilized time-lapse microscopy to monitor the mitotic index, duration of mitosis, and autophagosomes formation in cells during TTFields application. We found that the mitotic index in TTFields-treated cells was somewhat lower than in control group (60% and 73% of cell population, respectively), and that the duration of mitosis was longer in treated cells than in control cells (1.5 h vs. 1 h, respectively,  $p < 0.05$ ) (Supplementary Figure 3). These results are in accordance with previously published data, which demonstrated increased rates of mitotic catastrophe during TTFields application<sup>8,9</sup>. A robust increase in LC3-GFP puncta fluorescence was revealed in 51% of TTFields-treated cells relative to 17% in untreated cells (Fig. 4a, b). Through the analysis of multiple cells, we were able to identify mitotic events within a population and track autophagosome dynamics in the resulting daughter cells (Fig. 4c). Upregulation in LC3-GFP signal was detected in cells that exhibited visible signs of abnormal mitosis such as polyploid nucleus following slippage events (Fig. 4c, white arrow). An increased LC3-



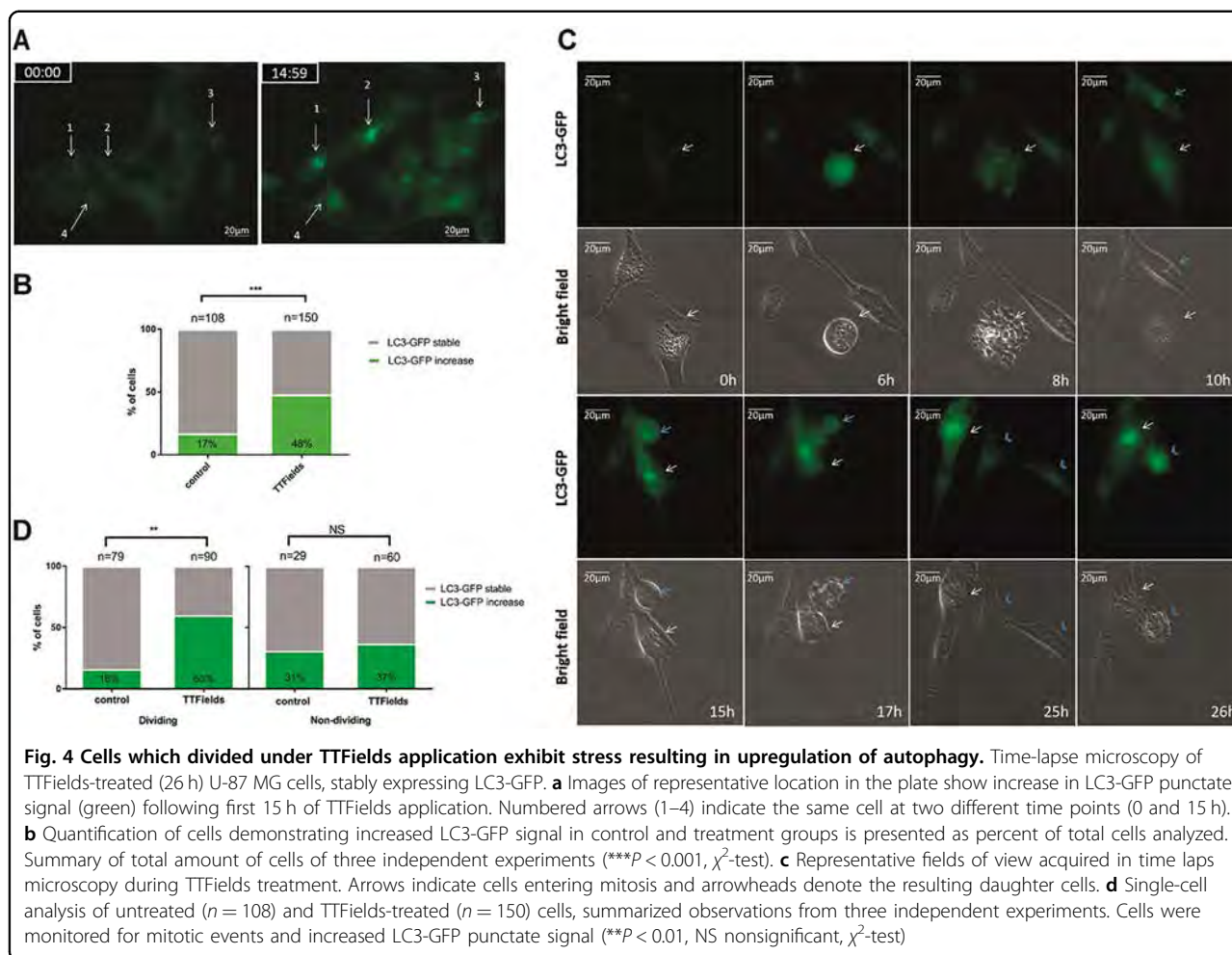


GFP signal was also detected in cells that had completed cytokinesis, but where the resulting daughter cells showed abnormal morphology (Fig. 4c, blue arrowhead). Most of the cells that divided during TTFields application showed increased LC3-GFP puncta (60%) relative to 16% of the dividing cells in the untreated culture (Fig. 4d, left). Percentage of cells that did not undergo mitosis, but showed increased LC3-GFP signal, was similar in control and TTFields group (Fig. 4d right). We conclude that the induction of autophagy following TTFields treatment is a consequence of aberrant mitosis.

#### TTFields-induced autophagy is mediated by AMPK activation

Aneuploidy-induced proteomic changes may generate proteotoxic stress, which is characterized by the engagement of protein degradation and folding pathways accompanied by additional energy requirements as reflected by low intracellular ATP levels<sup>29,30</sup>. We detected increased levels of GRP78 protein, a common marker of the endoplasmic reticulum unfolded protein response, in both A172 and U-87 MG cells treated with TTFields (Fig. 5a). In addition, intracellular ATP levels were found





to be reduced by 18% ( $p < 0.05$ ) in treated cells ( $\sim 1.2$  nmol for  $0.2 \times 10^6$  cells) relative to untreated ( $\sim 1.5$  nmol for  $0.2 \times 10^6$  cells) (Fig. 5b).

AMPK, a cardinal cellular energy sensor, is activated by various metabolic stresses and acts as a master positive regulator of autophagy by directly activating of the mammalian autophagy initiating kinase, ULK1<sup>31,32</sup>. Using immunoblot assay, we observed significantly elevated levels of phosphorylated AMPK in U-87 MG and A172 glioma cell lines treated with TTFields at the indicated time points (Fig. 5c, Supplementary Figure 4A). A sequential ULK1 activation indicated by Ser 317 phosphorylation (AMPK-specific site) was also noted (Fig. 5c, Supplementary Figure 4B).

Silencing of AMPK in U-87 MG cells, using small interfering RNAs (siRNAs; siAMPK) resulted in 80% reduction in AMPK protein levels and abrogated the increase in LC3-II levels in response to 48 h TTFields application (Fig. 5d). No changes in LC3-II protein level were observed even after the addition of CQ. Cells transfected with sham vector demonstrated elevated levels

of LC3-II after treatment with TTFields similar to U-87 MG wild-type cells (Fig. 5d left panel). Further validation using immunofluorescent staining revealed reduced prevalence of LC3 puncta in siAMPK-transfected cells relative to cells transfected with sham vector following 48 h of TTFields application (Fig. 5d right panel).

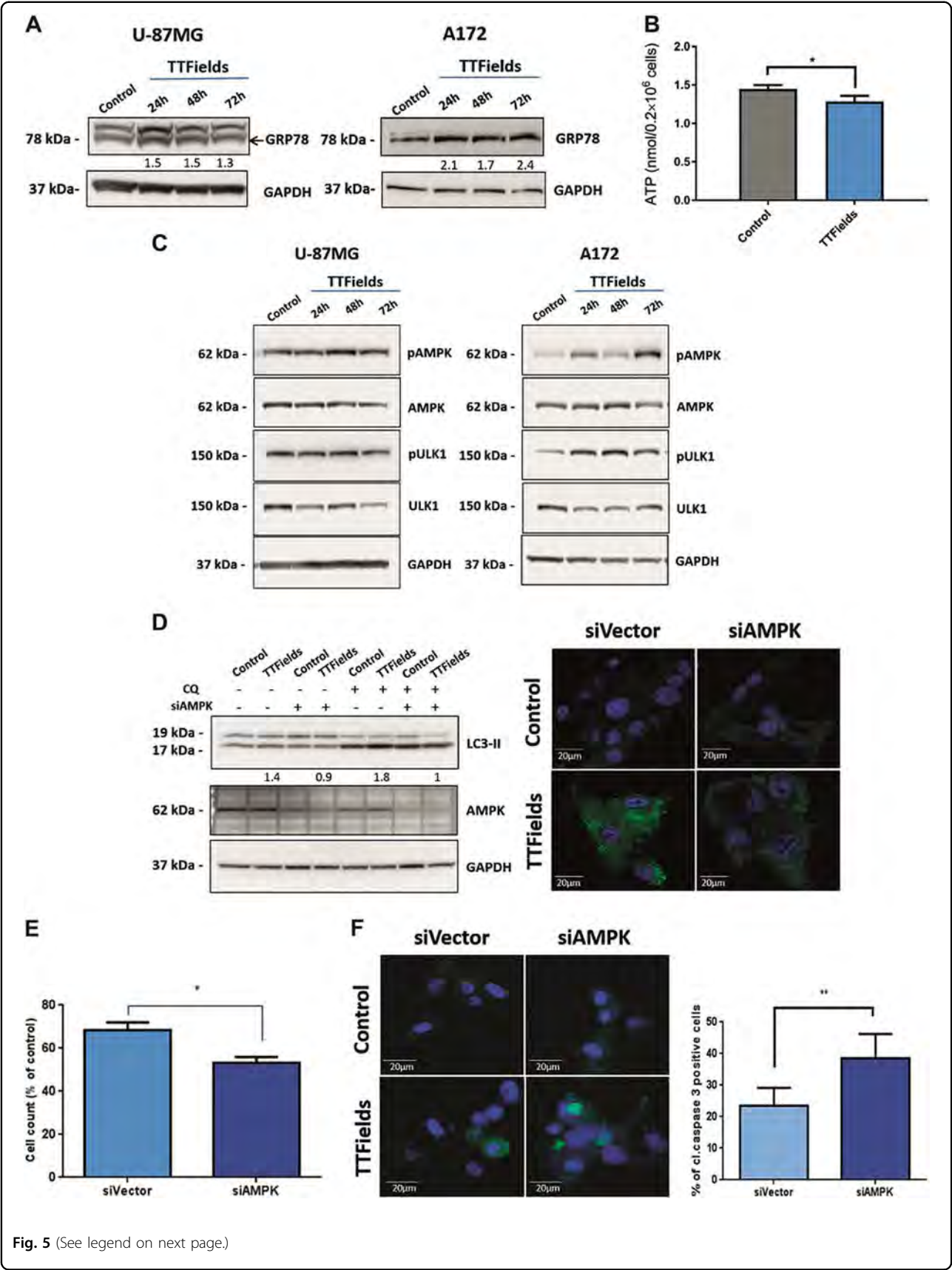
TTFields application for 48 h led to a significant reduction in the number of siAMPK cells relative to sham vector transfected cells (47% and 32% reduction in siAMPK and siVector, respectively) (Fig. 5e). The treated siAMPK cells demonstrated elevated levels of cleaved caspase-3 as seen by immunofluorescent staining (Fig. 5f).

Collectively, these results indicate that TTFields' upregulated autophagy is mediated through the AMPK pathway, and that inhibition of this pathway rendered the cells more susceptible to treatment.

#### Inhibition of autophagy enhances TTFields efficacy

TTFields-enhanced cytotoxic effect following AMPK silencing could be the outcome of an autophagy-independent processes, as AMPK regulates multiple







(see figure on previous page)

**Fig. 5 Induction of autophagy by TTFields is AMPK dependent.** **a** U-87 MG and A172 cells were either left untreated or were treated with TTFields for indicated time points. Immunoblot analysis of GFP78 protein. Numeric values represent the fold increase in GRP78 signal, normalized to loading control (GAPDH), relative to untreated control. **b** Quantification of intracellular ATP levels in U-87 MG cells either left untreated or treated with TTFields for 72 h. The results are presented as average ATP concentration (nmol/2 × 10<sup>6</sup> cells) from three independent experiments (\**P* < 0.01, Student's *t*-test). **c** U-87 MG and A172 cells were either left untreated or were treated with TTFields for indicated time points. Immunoblot analysis of pAMPK and pULK1 proteins. GAPDH was used as loading control. (5D-F) U-87 MG cells were transfected with AMPK-targeting siRNA (siAMPK) or with siRNA sham vector (siVector), and were incubated for 48 h with or without TTFields application. CQ 20 μM was added for the last 4 h of the treatment where indicated. **d** (left panel) Immunoblot analysis of LC3 and AMPK. Numeric values represent the fold-change in LC3-II signal, normalized to GAPDH signal, relative to respective control. **d** (right panel) CQ-treated cells were fixed and stained for LC3 (green) and DAPI (blue), original magnifications: × 40. **e** Cell count of siAMPK- or siVector-expressing cells after the TTFields treatment. (0.01 < \**P* < 0.05, Student's *t*-test, *n* = 3). **f** siVector- and siAMPK-transfected U-87 MG cells were either left untreated or were treated with TTFields for 48 h. Cells were then fixed and stained for cleaved caspase-3 (green) and DAPI (blue) (left panel). Images from each treatment were analyzed manually and the fraction of cleaved caspase-3 positive cells was calculated for at least 200 cells from each group (right panel) (\*\**P* < 0.01, Student's *t*-test, *n* = 2)

pathways. We utilized a genetic approach to specifically inhibit autophagy in cells using shATG7. Autophagy-related protein 7 (ATG7) is one of the key regulators of autophagosome formation and is responsible for conversion of LC3-I to LC3-II by phosphatidylethanolamine conjugation<sup>33</sup>. For this purpose, we generated lentiviral-mediated shATG7-expressing stable clones in U-87 MG and A172 cell lines. Inhibition of autophagy led to a significant decrease in cell numbers following 72 h of TTFields application relative to cells expressing sham vector (36% vs. 64% of cell reduction in shVector and shATG7 cells, respectively, in U-87 MG and 46% vs. 62% in A172) (Fig. 6a, Supplementary Figure 5). These results demonstrate that the inhibition of autophagy sensitizes glioma cells to TTFields treatment. Having established the necessity of autophagy for cell survival following TTFields application, we hypothesized that pharmacological targeting of autophagy could potentially provide a promising therapeutic strategy to circumvent resistance to TTFields. To test this, we combined TTFields with CQ in U-87 MG and A172 cells. We found that the combination treatment resulted in a significant reduction in cell numbers. Of note, this improvement in efficacy was observed even at low CQ concentrations (3 μM), whereas CQ monotherapy had no effect on cell counts (Fig. 6b). Flow cytometry analysis revealed higher levels of apoptosis (75%) in cells treated with TTFields in combination with low dose CQ (3 μM), whereas CQ monotherapy resulted in only 25% increase in apoptosis in A172 cells and 8% in U-87 MG cells (Fig. 6c). Overall, these findings suggest that glioma cells upregulate autophagy as a resistance mechanism to TTFields, and that pharmacological inhibition of autophagy circumvents this resistance and enhances the anti-mitotic effects of TTFields.

## Discussion

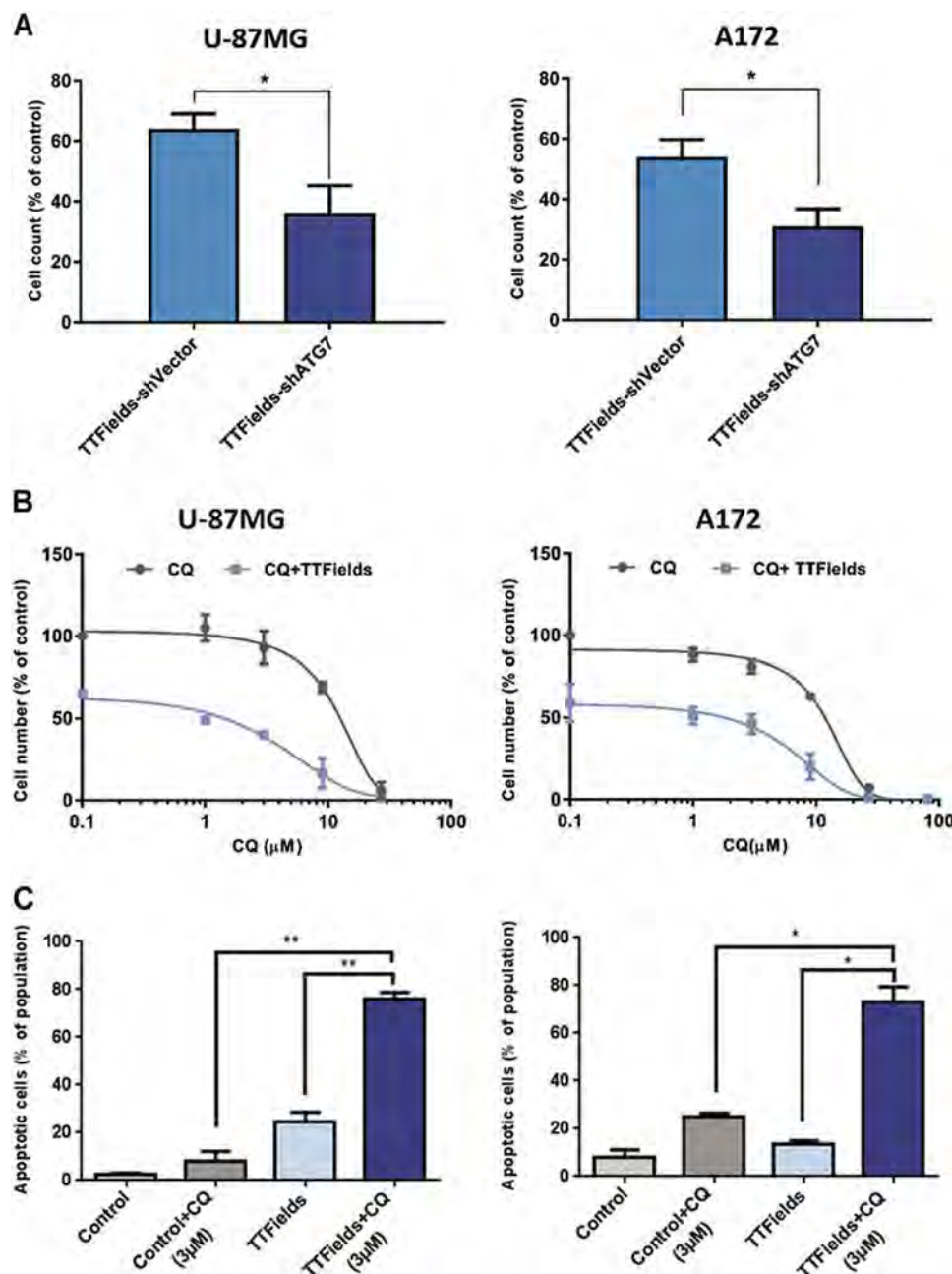
TTFields therapy is a physical treatment modality that has been demonstrated to improve both progression-free and overall survival in glioblastoma patients when added

to standard maintenance temozolomide chemotherapy<sup>4</sup>. Previous studies have demonstrated that TTFields exert an anti-mitotic effect by decreasing the fraction of polymerized tubulin during mitosis thus hampering normal spindle organization and producing severe structural mitotic deformities. These may lead to chromosome aneuploidy in the resulting daughter cells<sup>8</sup>. How cells survive the stress inflicted by TTFields is poorly understood. In this study, we demonstrate that daughter cells surviving TTFields application upregulate autophagy in response to proteotoxic stress, thereby promoting resistance to treatment (Fig. 7).

As TTFields act as a microtubule depolymerization agent, and as microtubules have an important role in both autophagosome transport and autophagosome-lysosome fusion, we speculated that the observed increase in autophagosome accumulation may result from interference in these processes, as demonstrated in cells treated with vinblastine (a known microtubule depolymerization agents)<sup>34</sup>. However, our results demonstrate successful autophagosomes-to-lysosome fusion under TTFields application, suggesting that such perturbation to the autophagy process is not inflicted by TTFields.

It is important to better understand how TTFields application promote autophagy in treated cells. It has been proposed that cells respond to aneuploidy by engaging proteotoxic stress response, which includes upregulation of pathways leading to the degradation of cellular constituents and protein folding<sup>30</sup>. Specifically, upregulation of autophagy was observed consistently in aneuploid cells<sup>28</sup>. We exploited single-cell analysis to show for the first time that TTFields application specifically triggers autophagy in the progeny cells that divided during treatment. This finding suggests that TTFields enhance autophagy in glioma cells as part of a cellular response to aberrant mitosis, with aneuploidy having a crucial role. Aneuploidy-induced proteomic change was previously shown to generate proteotoxic stress accompanied by



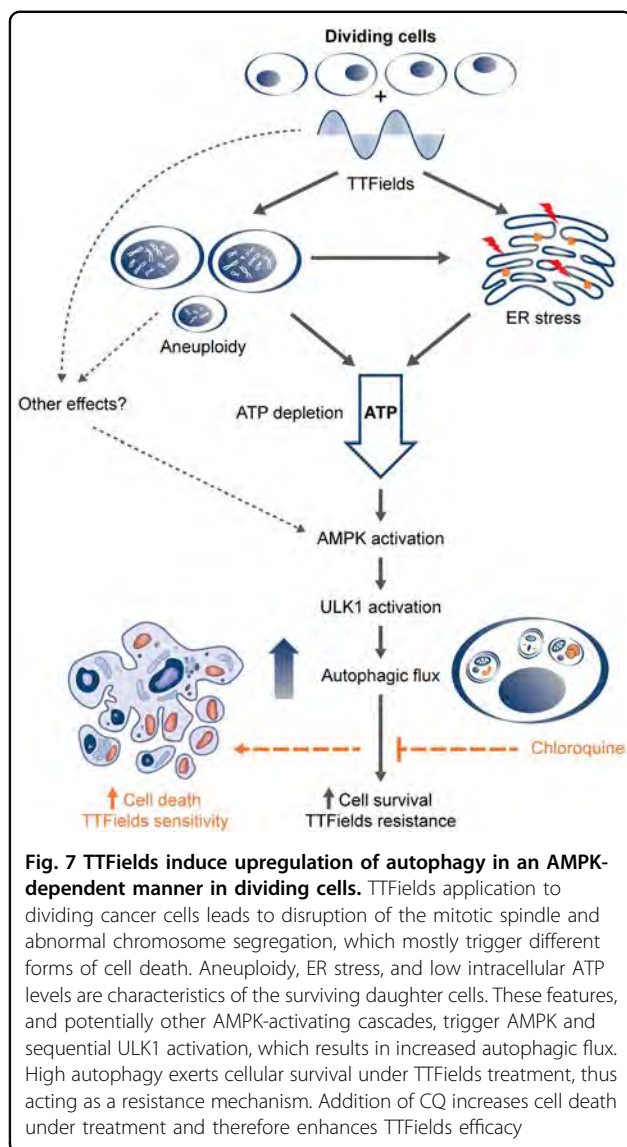


**Fig. 6** Autophagy inhibition triggers apoptosis and results in increased TTFIELDS efficacy in glioma cells. **a** U-87 MG and A172 were infected with lentiviral particle containing shATG7 or sham vector (shVector). Cells were then either left untreated or were treated with TTFIELDS for 72 h and enumerated by flow cytometry. The data are presented as percent of control. ( $0.01 < *P < 0.05$ , Student's *t*-test,  $n = 3$ ). **b**, **c** U-87 MG and A172 were treated for 72 h with CQ alone (1–27  $\mu$ M) and in combination with TTFIELDS. **b** Dose-response blots for U-87 MG (left) and A172 (right). **c** Fraction of apoptotic cells as indicated by Annexin V/7-AAD staining in TTFIELDS-treated vs. control cells, with or without CQ (3  $\mu$ M) ( $0.01 < *P < 0.05$ ,  $**P < 0.01$ , Student's *t*-test,  $n = 3$ )

additional energy requirements as reflected by low intracellular ATP levels<sup>29,30</sup>. We demonstrate that following TTFIELDS application, there is an increase in endoplasmic reticulum stress and reduced levels of intracellular ATP. Our data indicate that TTFIELDS-induced autophagy is

mediated and dependent on AMPK activity, which is in line with the observed proteotoxic stress response and reduced ATP intracellular levels, as AMPK is activated by low-energy status. Therefore, we propose that autophagy is triggered via AMPK activation in response to aneuploid





status following cell division under TTFIELDS application (Fig. 7).

It is noteworthy that Karanam et al.<sup>11</sup> have recently shown that TTFIELDS can potentially induce replication stress and reduction of BRCA1 pathway proteins, eventually leading to genotoxic stress.

Therefore, in addition to aneuploidy, AMPK-dependent induction of autophagy can also be potentially triggered by such genotoxic stress. For example, the serine/threonine kinase ATM, which is a major sensor of DNA double-strand breaks, can activate AMPK, thus leading to induction of autophagy<sup>35,36</sup>. Another example is the DNA damage repair enzyme PARP1, which is associated with elevated AMP levels that activate AMPK<sup>37</sup>. In the present study, we have not examined whether these pathways are activated following TTFIELDS application and future

studies are needed to assess the contribution of TTFIELDS-induced genotoxic stress to autophagy.

Induction of autophagy in normal tissue may exert a detrimental effect and lead to autophagic cell death<sup>38,39</sup>. Effective TTFIELDS intensities are present not just in the tumor but also in the surrounding tissues and may potentially affect normal bystander cells. However, both preclinical and clinical evidence did not reveal adverse events in normal tissues. Our findings demonstrate that the upregulation of autophagy by TTFIELDS is restricted to dividing cells, which may explain the relatively lack of safety issues with this modality.

Extensive preclinical evidence for the involvement of autophagy in cancer cell survival has led to a rise in clinical trials, which are underway to evaluate the therapeutic potential of autophagy inhibitors in combination with chemotherapy<sup>18,40,41</sup>. A preclinical glioma model showed that autophagy upregulation in response to temozolomide confers resistance to treatment<sup>42</sup>. Although TTFIELDS differ significantly in their mode of action from chemo and radiotherapy, our data indicate a similar resistance pattern of cells utilizing autophagy to evade lethal effects. Specifically, our results demonstrate that blocking autophagy induced by TTFIELDS by using either genetic or pharmacologic approaches, results in increased treatment efficacy. CQ and its derivative hydroxychloroquine, a broadly used anti-malarial agent, are currently the only clinically available drugs to inhibit autophagy<sup>43</sup>. In our study, combination of TTFIELDS with CQ resulted in decreased cell viability in a dose-dependent manner. Moreover, the presence of low concentration of CQ, which has no effect on cell number as a monotherapy, resulted in high levels of apoptosis when combined with TTFIELDS (Fig. 7). These results indicate increased treatment efficacy for the combined treatment and provide strong rationale for additional in-vivo studies.

Interestingly, a recent study by Silginer et al.<sup>17</sup> demonstrated that the concomitant use of 3-Methyladenine (3-MA; early-stage inhibitor of autophagy) during TTFIELDS application result in higher cell viability. 3-MA is known to block class I and class III PI3K activity, thus exhibiting dual activity that could lead to either inhibition or upregulation of autophagy<sup>44</sup>. Targeting a complex process such as autophagy may lead to different consequences depending on the exact stage of autophagy being targeted. It has been reported that in treatment regimens utilizing cytotoxic drugs combined with agents that inhibit autophagy at an early stage, the cytotoxic effect was hindered. On the other hand, inhibition at late stages in autophagy (e.g., using bafilomycin or CQ) led to enhanced efficacy of the same treatment as reflected by increased cytotoxic effect, suggesting that accumulation of autolysosomes is necessary for cell death induction<sup>45,46</sup>. Although CQ is primarily acknowledged as



blocker of lysosomal degradation, a recent study by Mauthe et al.<sup>47</sup> demonstrated that CQ can also inflict severe disorganization of the Golgi and endo-lysosomal systems. Therefore, it is imperative to also acknowledge the autophagy-independent effects of CQ and the possibility that some elements of the enhanced treatment efficacy of the combined treatment with CQ may be attributed to other autophagy-unrelated cellular alterations.

The combination of CQ with two additional drugs, 17-allylamino-17-demethoxy-geldanamycin and 5-aminoimidazole-4-carboxamide riboside, had been shown to promote proteotoxic and metabolic stress leading to the induction of apoptosis exclusively in aneuploid cells<sup>27</sup>. Future work is warranted on these and other therapeutic combinations that could leverage the stress response induced by TTFields, to further enhance treatment efficacy.

## Materials and methods

### Cell lines and cultures

All cell lines were obtained from ATCC: MSTO-211H (human biphasic mesothelioma), KLN-205 (murine squamous cell carcinoma), LLC-1 (murine Lewis lung carcinoma), AsPC-1 (pancreatic adenocarcinoma), A172, U-87 MG, LN229 (human glioma cell lines), and F98 (rat glioma). Cells were cultured in Dulbecco's modified Eagle's medium (Biological Industries) or RPMI (GIBCO) medium supplemented with 10% fetal bovine serum and antibiotics.

### TTFields application

TTFields were applied to cell cultures using the inovitro™ system (Novocure Ltd) as described<sup>48,49</sup>. Cells were seeded on cover slips at a density of 5000–20,000 cells in 500 µL and treated at predetermined optimal frequencies: MSTO-211H (150 kHz), KLN-205 (150 kHz), LLC-1 (150 kHz), AsPC-1 (150 kHz), A172 (200 kHz), U-87 MG (200 kHz), LN229 (200 kHz), and F98 (200 kHz) at the same nominal intensity (1.75 V/cm RMS). TTFields were applied from two directions, which were changed by 90° every 1 s as previously described<sup>3</sup>. Culture media (2 ml per dish) was replaced every 24 h for all control and treatment dishes.

### Flow cytometry

To assess cellular granularity, cells treated with TTFields for 72 h were analyzed based on their side-scatter values. Evaluation of treatment efficacy was quantitatively determined by cell count after specified treatment duration. The relative number of cells at the end of treatment was expressed as a percentage of untreated control. For detection of apoptosis, cells were double-stained with fluorescein isothiocyanate-

conjugated Annexin V (MEBCYTO 4700 Apoptosis Kit; MBL) and 7-Aminoactinomycin D (BioLegend) as per the manufacturer's instructions. Data acquisition was obtained using iCyt EC800 (Sony Biotechnology) flow cytometer.

### LysoTracker staining

Cells were stained for 80 min in 37 °C with 75 nM LysoTracker probe (Molecular Probes). Images were obtained using upright motorized microscope with × 40/0.75 objective (ZeissAxio Imager Z2) equipped with the Orca R2 camera (Hamamatsu Photonics, Japan).

### Immunocytochemistry

For autophagy assessments, cells were grown on glass cover slips and treated using the inovitro™ system (Novocure, Israel) for 48 h. At the end of the treatment, cells were fixed with ice-cold methanol for 10 min. The cells were then serum-blocked and stained with microtubule-associated protein 1 LC3 (rabbit polyclonal, Novus) and LAMP1 antibody (mouse monoclonal, Santa Cruz). Alexa Fluor 488- or 533-conjugated secondary antibody was used (Jackson ImmunoResearch). DNA was stained with the dye 4',6-diamidino-2-phenylindole (DAPI) (Sigma-Aldrich) at 0.2 µg/ml for 20 min. Images were collected using a LSM 700 laser scanning confocal system, attached to an upright motorized microscope with × 63/1.40 oil objective (ZeissAxio Imager Z2). To better detect LC3 by immunofluorescence, cells were cultured in the presence of CQ diphosphate (Sigma) (CQ, 20 µM) during the last 3 h of the treatment. CQ was applied to both control and TTFields-treated cells. Colocalization of LAMP1 and LC3 was tested in three individual cells from each treatment using the profile tool in the Zen 2.3. software (Blue edition; Carl Zeiss Microscopy, GmbH). Areas in which at least two LC3 foci were apparent were used for the analysis. For cleaved caspase-3 staining following treatment, cells were fixed with paraformaldehyde (PFA) 4%, permeabilized with 0.3% Triton solution in phosphate-buffered saline (PBS) (× 1), and stained with anti-cleaved caspase-3 antibody (rabbit polyclonal, Cell Signaling). The quantification of intensity of green signal, reflecting amount of LC3-positive puncta, was carried out using ImageJ software and presented as percentage of average intensity per cell normalized to average intensity in untreated cells. The quantification of cleaved caspase-3-positive cells was done manually in a blinded manner. The data were presented as percent of positive stained cells.

### Cell lysates and immunoblotting

Cell extracts were prepared using RIPA lysis buffer containing 150 mM sodium chloride, 1% NP-40, 0.1% SDS, 50 mM Tris pH = 8, supplemented with a cocktail of



protease (Complete Mini, Roche), and phosphatase inhibitors (Thermo Scientific). After determining protein concentration (Bradford reagent, Bio-Rad), 30 µg protein were resolved by SDS-polyacrylamide gel electrophoresis under reducing conditions. After electrophoresis, proteins were transferred to polyvinylidene difluoride membrane (Bio-Rad) and probed with the appropriate primary antibody: LC3 (NB600-307) purchased from Novus, pAMPK (2535), AMPK (2793), pULK1 (12753), ULK1 (8054), pP70 (9205s), ATG7 (8558) from Cell Signaling; GAPDH (SC-32233), GRP78 (BiP) (SC-376768) from Santa Cruz; Vinculin (V9131) from Sigma-Aldrich followed by horseradish peroxidase-conjugated secondary antibody (Abcam ab6721, ab97023), Rockland (111-035-144), and a chemiluminescent substrate (Millipore).

#### siRNA-mediated knockdown of Ampk

U-87 MG cells were transfected with siRNA specific for Ampk (SMARTpool: ON-TARGETplus Human PRKAA1 siRNA, Dharmacon) using Lipofectamine (Invitrogen, Life Technologies Corporation) according to the manufacturer's instruction. Cells were seeded on cover slips in invitro dishes 24 h before transfection. At the time of the experiment, the cells had reached 50% confluency. The culture medium was replaced with Opti-MEM (Invitrogen) containing 20 nM of siRNA mixed with 1 ml of Dulbecco's Modified Eagle antibiotics-free medium and 10 µl of RNAi-Lipofectamine 2000. After 48 h, dishes were connected to the invitro systems and TTFIELDS were applied for 48 h.

#### Time-lapse microscopy

U-87 MG cells were transfected with pSELECT-GFP-hLC3 vector (InvivoGen) using Lipofectamine (Invitrogen, Life Technologies Corporation) according to the manufacturer's instruction. Following transfection, cells were washed and selected for resistance to zeocin (600 µg/ml) (InvivoGene). Stable transfected cells were observed for 24 h using time-lapse series microscopy (ZeissAxio Observer; × 10 objective) either with or without TTFIELDS. TTFIELDS (1.75 V/cm) were applied using the invitro Live™ system (Novocure). Briefly, two pairs of transducer arrays were printed perpendicularly on the outer walls of a cylinder invitro Live insert composed of high dielectric constant ceramic [lead magnesium niobate–lead titanate]. The transducer arrays were connected to a sinusoidal waveform generator that generated the electric fields in the medium. The orientation of the TTFIELDS were switched 90° every 1 s, thus covering the majority of the orientation axis of cell divisions as previously described by Kirson et al.<sup>3</sup>. Temperature was measured by 2 thermistors (Omega Engineering, Stamford, CT) attached to the ceramic walls. Cells were grown in high Glass Bottom 35 mm µ-Dish (Ibidi, GMBH). The invitro Live insert

was placed inside the glass bottom dish. Image stacks were acquired every 15 min.

#### Time-lapse microscopy data analysis

Single cells were followed manually by two independent investigators. Mitotic events were recorded in a blinded manner. Images of cells before and after mitosis were analyzed using ImageJ software (NIH) as described by Veldhoen et al.<sup>50</sup>, and modified to accommodate single-cell analysis. Briefly, puncta were identified by generating surfaces in ImageJ after background subtraction (Rolling Ball Background, rolling = 20) and setting of identical threshold to all images. The fluorescence intensity localized to all puncta in each cell after mitosis were divided by the fluorescence intensity measured in the same cell before mitosis. A threshold value of twofold increase in LC3-GFP fluorescence intensity relative to the initial state of the cell was defined as “increased.” For non-dividing cells, images from the beginning and the end of treatment were analyzed and compared in the same manner.

#### Electron microscopy

A172 and U-87 MG cells, control or treated with TTFIELDS for 48 h, were fixed in PFA (3%) + glutaraldehyde 2.5% + 0.1 M cacodylate buffer + 5 mM CaCl + 3% sucrose and further processed for blocking and section preparation. Thin sections (70 nm) were coated with carbon and visualized using Zeiss Ultra-Plus FEG-SEM equipped with transmission electron detector, at acceleration voltage of 30 kV. In addition, U-87 MG cells control or treated, in the presence of CQ (1 µM, 24 h) (Sigma-Aldrich), were fixed as described and were visualized using JEOL JEM-1011 TEM. Count of autophagic vacuoles was performed manually in a blinded manner.

#### shRNA lentiviral infection

Human ATG7 short hairpin RNA (shRNA) and non-silencing-GIPZ lentiviral shRNAmir control were purchased from Dharmacon. shATG7 containing viral particles were produced using LENTI-Smart kit (InvivoGen), according to the manufacturer's instruction, in 293T cells. U-87 MG and A172 cells were infected with lentiviral particles; 24 h after infection, cells were washed and selected for puromycin (Sigma) (2 µg/ml) resistance for 3 days. ATG7 protein levels in stable culture were further validated in western blot analysis with specific anti ATG7 (rabbit monoclonal, Cell Signaling) antibody.

#### ATP measurement

ATP intracellular levels were measured with colorimetric ATP assay kit (Abcam) according to the manufacturer's instructions. After 48 h of treatment, cells were collected and  $1 \times 10^6$  cells from each sample were resuspended in ATP lysis buffer. Trichloroacetic acid (100%)



was used for sample deproteinizing followed by neutralization step KOH (1 M). ATP reaction mix and background control (50  $\mu$ L) was added to the wells and incubated for 30 min in dark, followed by an absorbance measurement at 550 nm using an ELISA reader (infinite F200, Tecan).

### In-vivo application of TTFields

All animal studies were approved by the Novocure Internal Animal Care Committee in accordance with the Technion-Israel Institute of Technology guidelines for the care of laboratory animals. Twelve-week-old Male Fischer rats (Harlan Laboratories, Israel) were inoculated stereotactically into the subcortical white matter in the right hemisphere with glioma (F98) cells ( $1 \times 10^4$ ), as previously described<sup>2</sup>.

Rats were allowed to recuperate for 7 days before treatment initiation. Application of TTFields (200 kHz) to the rat brain was initiated 7 days after intracranial tumor inoculation and was maintained for 7 days. Two pairs of electrodes, each composed of two disks with a radius of 3 mm, were attached to the rat skull in dorsolateral and left–right positions generating two different field directions. The capacitance of each disk was about 30 nF. Each disk contained a thermistor in order to allow for constant temperature monitoring. The current source output was switched, every 1 s, between the two electrodes. Control rats were treated by means of sham electrodes, which were geometrically matched to the TTFields group. The Sham heat electrodes produced equal temperature changes to those produced by the field electrodes by means of a heating resistor incorporated within them. Each rat was placed inside a separate cage and the electrodes were connected to the NovoTTF-100A<sup>TM</sup> device. Rats were checked twice daily for their physical condition. At the end of treatment, the rats were killed and the tumors were removed.

### Immunohistochemistry

For immunofluorescent staining, paraffin-embedded tumor sections were deparaffinized with HistoChoice (Sigma-Aldrich) and rehydrated with graded alcohol treatments. Antigen retrieval was carried out by microwave treatment for 22 min in citrate buffer (pH 6.0). Sections were blocked in 10% normal goat serum in PBS and incubated overnight with primary antibody (LC3, Novus) following secondary antibody (Alexa Flour 488, Jackson ImmunoResearch) incubation and DAPI for nuclei counterstaining. The whole slide image was collected using Automatic slide scanner 250 Flash (3DHIS-TECH). The quantification of intensity of green signal, reflecting amount of LC3 staining, was carried out using CaseViewer following ImageJ software. Three different areas of similar size from each image were chosen in a

blinded manner to be analyzed by ImageJ software. Average green intensity per image was calculated. The data are presented as average intensity relative to control in each set of staining.

### Statistical analysis

Data are presented as means  $\pm$  SE. Statistical significance was analyzed by the two-tailed Student's *t*-test.  $\chi^2$ -analysis was applied to determine significant relationship between mitosis and TTFields treatment (GraphPad Prism 6 utility software). Values of  $P < 0.05$  were considered significant. All experiments were repeated at least three times with similar results.

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### Conflict of interest

We wish to disclose that Y. Palti holds stock in Novocure Ltd. A.S., Y. Porat, T.V., R.S.S., M.M., E.Z., N.K., K.G., M.G., E.D.K., A.K., and U.W. are paid full-time employees of Novocure, and all authors hold Novocure stock options. The authors declare that they have no conflict of interest.

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RESEARCH

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# Dosimetric impact of tumor treating field (TTField) transducer arrays onto treatment plans for glioblastomas – a planning study

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## Abstract

**Background:** Tumor-Treating Fields (TTFields) are a novel treatment strategy for glioblastoma (GBM) that is approved for the use concomitantly to adjuvant chemotherapy. Preclinical data suggest a synergistic interaction of TTFields and radiotherapy (RT). However, the dosimetric uncertainties caused by the highly dense arrays have led to caution of applying the TTF setup during RT.

**Methods:** In a RW3 slab phantom we compared the MV- and kV-CT based planned dose with the measured dose. VMAT-plans were optimized on MV-CTs of an Alderson head phantom without TTF arrays and then re-calculated on the same phantom equipped with TTF arrays. Dose at organs at risk (OAR) and target volumes (PTVs) were compared.

**Results:** Measurements at a depth of 2, 3 and 4 cm of a RW 3 slab phantom show an attenuation due to TTField arrays of 3.4, 3.7 and 2.7% respectively. This was in-line with calculated attenuations based on MV-CT (1.2, 2.5 and 2.5%) but not with the attenuation expected from kV-CT based calculations (7.1, 8.2 and 8.6%). Consecutive MV-CT based VMAT planning and re-calculation reveals, that the conformity and homogeneity are not affected by the presence of TTField arrays. The dose at organs at risk (OAR) can show increases or decreases by < 0.5 Gy, which should be considered especially in cases next to the skull base.

**Conclusion:** MV-CT based dose calculation results in reliable dose distributions also in the presence of TTField arrays. There is a small but clinically not relevant interaction between the TTField arrays and VMAT dose application. Thus, daily replacement of TTField arrays is not necessary in regard to deeply located OARs. RT is feasible, when a VMAT treatment plan is optimized to an array free planning CT. As the biologic effect of a concomitant treatment especially on OARs is currently unknown, a concomitant treatment should be performed only within clinical trials.

## Background

Alternating electric fields (tumor-treating fields, TTFields) are a novel treatment strategy for several malignancies, which has shown a stand-alone efficacy comparable to chemotherapeutic agents in recurrent glioblastoma (GBM) [1]. Also in primary GBM a significant benefit for patients treated with TTFields as a concomitant treatment during adjuvant chemotherapy is evident [1–3]. Based on these

results, the Optune® system (Novocure) gained FDA approval for the treatment of recurrent GBM in 2011 and for the treatment of newly diagnosed GBM in 2015 [4]. In Europe, Optune gained a CE certification in 2015. Furthermore, TTFields were included into the NCCN guidelines for the treatment of primary as well as recurrent GBM as one treatment option [5].

The pathophysiological background of TTFields is still under investigation. However, a prolongation of the cell division, probably elicited by the interference of the alternating electric fields with the condensation of polar tubulin molecules leading to an interruption in spindle formation, seems to be one hallmark of the effect [2, 4, 6, 7]. As a consequence, cells that are exposed to TTFields accumulate

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within the G2/M-phase; notably, this phase is also associated with a significant vulnerability for radiation induced DNA damages [4, 7]. Besides differences between the proliferation rates of normal tissue cells and tumor cells, TTFIELD effects were described to be frequency dependent [2]. A theoretical synergistic effect of radiation and TTFIELDS was recently corroborated by the results of several preclinical studies, investigating the efficacy of a concomitant treatment with radiation and TTFIELDS in lung cancer and GBM cell lines [6–8]. The increased rate of cell death reported by these articles was explained by an impairment of double-strand break repair, the down-regulation of angiogenesis and invasion—related markers such as VEGF and MMP9 also point towards an impaired migration [6, 8]. Furthermore, within the context of chemotherapies, an earlier onset of effective treatments has shown an advantage over use of these therapies within a salvage treatment in low grade glioma as well as in GBM and Medulloblastoma [9–12].

When a synergistic effect of TTFIELDS and radiation seems to be possible, the mode of practically combining these modalities should be investigated. Generally spoken, there are two options of combining a radiotherapy to a TTFIELD treatment. First of all, one could detach the TTFIELD arrays before each fraction and re-attach a new set of arrays afterwards. This strategy would rule out any influence of the TTFIELD arrays onto the dose distribution and an increase of the dose at the organs at risk. On the other hand, a daily change of the arrays could lead to skin irritation and might be associated with longer intervals of de-activated TTFIELDS, with possible negative effects of its efficacy [13]. Additionally, increasing the frequency of array-changes would increase the costs, too. Another strategy would be to leave the arrays attached to the skull during radiotherapy. This strategy could be associated with an increased skin toxicity due to a previously prescribed bolus effect [14]. On the other hand, avoiding to change the arrays on a daily basis could increase the treatment compliance and would possibly reduce the treatment costs. Furthermore, since the TTFIELD transducer arrays consist of materials with a high physical density, there was considerable concern that array application during RT might influence the dose delivery to the patient. Additionally, image artefacts could interfere with the re-positioning of patients. Therefore, before any study concepts with RT and concomitant TTFIELDS are initiated, we focussed to determine any potential interactions between TTFIELD arrays and RT in terms of calculated dose and dose distribution.

## Methods

We first performed a planning study using RW3 water equivalent slabs as a phantom (PTW GmbH, Freiburg, Germany). The phantom was equipped with and without a

Novocure Optune TTFIELD array. TTFIELD arrays consist of 9 transducer arrays which each have a thickness of 2.5 mm, a diameter of 2 cm and a physical density of 7.75 g/cm<sup>3</sup>. The electron density (ED) of the arrays as well as the exact chemical composition is unknown. The whole setup was scanned with a Somatom Emotion CT-scanner (kV-CT, 1 mm slice thickness, voxel size 1 × 1 × 1 mm<sup>3</sup>, 130 kV; Siemens Medical Solutions, Erlangen, Germany) and with a TomoTherapy using its MV-CT function (2 mm slice thickness, voxel size 2 × 0.8 × 0.8 mm<sup>3</sup>, 3.5 MV; Accuray Inc., Sunnyvale CA, USA). Irradiation of the RW3 slab phantom was simulated with the treatment planning system (TPS) Eclipse 13.0 (Varian Medical Systems, Palo Alto, CA, USA) using an 0°, 15 × 15 cm<sup>2</sup>, 6 MV photon field with 200 MU. Hounsfield units (HU) were converted to ED based on two different HU-ED conversion tables, then calibrated for the MV-CT and the kV-CT, respectively. We are using kV- as well as MV-CT based treatment planning, the latter one for instance in cases with both sided hip replacements, within the daily clinical routine at our facility. The dose was calculated based on the kV-CT and the MV-CT of the phantom with the AAA13 algorithm. No additional density correction was applied to correct for artefacts or the density of the TTFIELD arrays.

The calculated dose was compared to measurements from irradiating an identical field (15 × 15 cm<sup>2</sup>, 6 MV, 200 MU) to the RW3 slab phantom with and without a TTFIELD array. Measurements were performed on a Trilogy linear accelerator (Varian Medical Systems, Palo Alto, CA, USA). The dose at 2, 3 and 4 cm depth was detected by a 2D diode detector array (MapCheck2, SunNuclear Corp., Melbourne, FL, USA). In all measurements, the TTFIELD device was not connected to a field generator when radiation was applied, as effects of the fields on secondary electrons currently cannot be estimated within any planning system and as a radiation induced damage of the portable field generator cannot be excluded. Therefore, only the passive effect of the TTFIELD arrays can be presented. Each measurement included three technical replicates. The attenuation caused by the TTFIELD arrays was calculated as ratio between the dose without the arrays and the dose with the arrays attached to the uppermost RW3 slab. The attenuated dose was measured within the 71 diodes directly below the TTFIELD arrays and was compared to 71 reference points in the same position of the treatment plans. A difference between measurements and dose calculations of < 3% was deemed to be clinical acceptable.

According to the treatment recommendation of TTFIELDS, the position of the TTFIELD arrays have to be changed every 3 days in order to reduce skin irritations caused by the contact gel below the electrodes. To account for this, the Alderson head-phantom was first scanned with kV-CT and MV-CT without the TTFIELD arrays, and thereafter with four TTFIELD arrays in two different positions (Position “A”



and “B”). Each setup included four TTField transducer arrays, with two arrays in opposing positions (i.e. anterior-posterior) while the two remaining arrays were positioned orthogonally (i.e. bi-temporal) (Additional file 1: Figure S1).

Two target volumes were generated to investigate for two distinct questions. PTV1 would have represented a parietal glioblastoma, a location where almost the entire PTV lies within CT slices that are covered by a large number of electrodes. This volume was chosen to investigate whether the electrodes would lead to impairments within the dose distribution to the target volume. PTV2 simulates a temporopolar glioblastoma. Due to its position next to the skull base, irradiation of such volumes often is a trade-off between the dose coverage of the PTV and the dose of the organs at risk, namely the optical nerves, the chiasm and the brainstem. This volume was chosen to investigate, whether the addition of electrodes could lead to an overdosing within the OARs. The effect on the dose distribution caused by the electrodes applied to the head was evaluated by optimizing volumetric arc treatment plans (VMAT) with two arcs with 6 MV for the two PTVs on the MV-CT of the Alderson phantom without electrodes. Subsequently, this plan was copied and recalculated onto MV-CTs of the Alderson phantom with four TTField arrays placed onto the head in position A and B, corresponding to the clinical use of the arrays. The amount of monitor units (MU) was identical for all three plans. The resulting dose distributions were compared according to the ICRU 83 report recommendations by comparing conformity (defined as  $CI = V_{95\%}/PTV$ ), homogeneity (defined as  $HI = (D_{98\%} - D_{2\%})/D_{50\%}$ ),  $D_{min}$ ,  $D_{98\%}$ ,  $D_{mean}$ ,  $D_{50\%}$ ,  $D_{2\%}$ ,  $D_{max}$  of the PTV as well as according to the  $D_{mean}$ ,  $D_{max}$ ,  $D_{2\%}$ ,  $V_{50Gy}$  and  $V_{54Gy}$  of the OARs [15].

To investigate the impact of the TTField arrays on image quality and registration, we compared kV-CTs, MV-CTs and kV cone beam CTs (CBCT) of the Alderson head phantom with TTField arrays. The latter was acquired using the kV on-board imaging system of the Varian Trilogy.

## Results

### RW3 slab phantom

kV-CT based scanning results in significant artefacts within the slices involving the arrays. Due to their high physical density the mean CT-value of the arrays is 3069 HU (SD 1.1), which is limited due to the maximum representable HU value of 3071 HU in our kV-CT scanner. The images were affected by several artefacts, including a feigned thickness of 7 mm and a large halo below and above the arrays onto which a CT-Value of > 1000 HU is projected (Fig. 1a, right panel).

MV-CT-scanning resulted in almost artefact free images (Fig. 1a, left panel). The TTField transducer arrays were

represented by a mean density of 2437 HU (SD 134) and were depicted slightly thicker than real (3.6 mm) but with an accurate structure. The difference in thickness, however, can also be caused by the lower z-resolution of the MV-CT.

Comparing the dose calculated on the RW3 slab phantom with and without TTField array to the doses measured in 2, 3 and 4 cm of depth, kV-CT calculation resulted in a dose attenuation by the electrodes of 7.1, 8.2 and 8.6%. The dose calculation based on the MV-CTs resulted in an attenuation of 1.2, 2.5 and 2.5% in 2, 3 and 4 cm, respectively. The dose measurement of the same setup in the same depths with the MapCheck2 diode array resulted in an attenuation of 3.4, 3.7 and 2.7% (Fig. 1b, Table 1). When the doses at 2, 3 and 4 cm of MV-CT based or kV-CT based calculations were compared to the measured doses at the specific depths, this resulted in a difference of 2.2, 1.1 and 0.05% or – 4.2, – 5.0 and – 6.9%, respectively.

A 5 mm area below the electrodes showed an increase in the local dose by 23.7% ( $D_{mean}$ ) and 1.0% ( $D_{max}$ ) for MV-CT and 10.4% ( $D_{mean}$ ) and 3.3% ( $D_{max}$ ) for kV-CT, respectively, indicating a bolus effect of the electrodes. This changes could not be verified with the MapCheck2 system, as the minimum depth for measurements with this system is 2 cm.

### Alderson head phantom

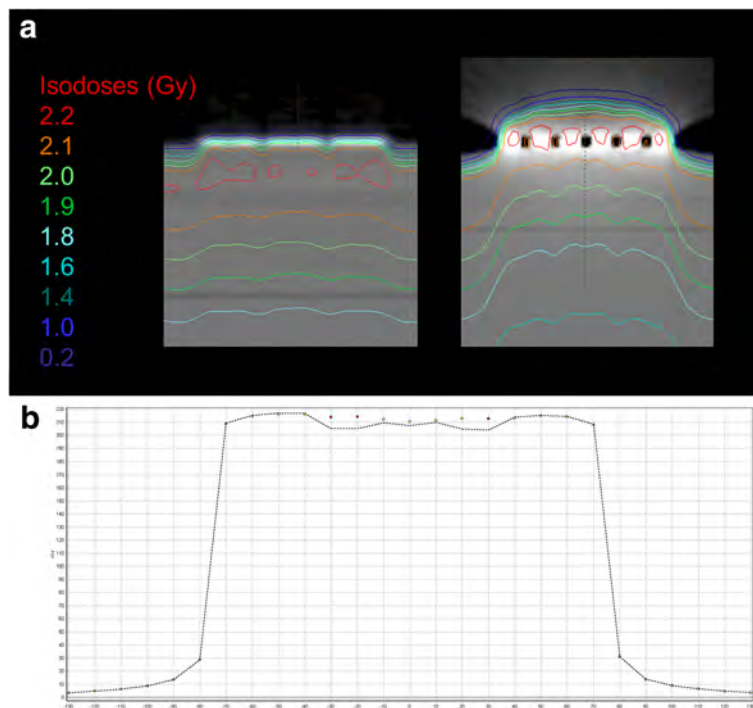
As expected from the results from the RW3 slab phantom scans, kV-CTs and CBCTs of the head phantom suffered from a large burden of artefacts in the slices that involved electrodes (Fig. 2). Due to the higher photon energy there were almost no artefacts present in the MV-CT. Bony structures from the skull base were clearly visible in all modalities. When the registration was based on the bony structures of the phantom, including the skull base, registration of the images was not affected by the presence of the TTField arrays.

In both PTVs, the addition of TTField arrays led to a negligible reduction of the conformity and minor changes of the mean and maximum dose up to 1.0 Gy (Figs. 3 and 4, Tables 2 and 3). In the presence of TTField arrays,  $D_{min}$  was up to 4.4 Gy lower as compared to plans without TTField arrays. The volume compromised by this decrease had a size of 0.05 cm<sup>3</sup>. No changes in the homogeneity of the dose distribution were found. The OARs, namely the optical nerves, the chiasm and the brainstem, were mostly stable or decreased (Tables 2 and 3). The largest increase was observed at the optic nerves, where an increase of up to 0.4 Gy was present.

## Discussion

In the present work, we used MV-CT based treatment planning and re-planning to investigate changes in the





**Fig. 1** **a** MV-CT (left side) and kV-CT (right side) of a RW3 slab phantom equipped with a NovoCure Optune TTField array planned for a  $15 \times 15$  cm<sup>2</sup> 0° 6 MV 200 MU photon beam. **b** For verification of the dose calculation, the dose in 2 cm depth was measured in the same setup with and without a TTField array at the surface of a RW3 slab phantom. The dots represent the measurement without the TTField array, the dashed line represents the measurements with TTField

dose delivery introduced by high density TTField arrays. This information is prerequisite for establishing study protocols that can investigate the safety and efficacy of a concomitant use of TTFields during a course of radiotherapy.

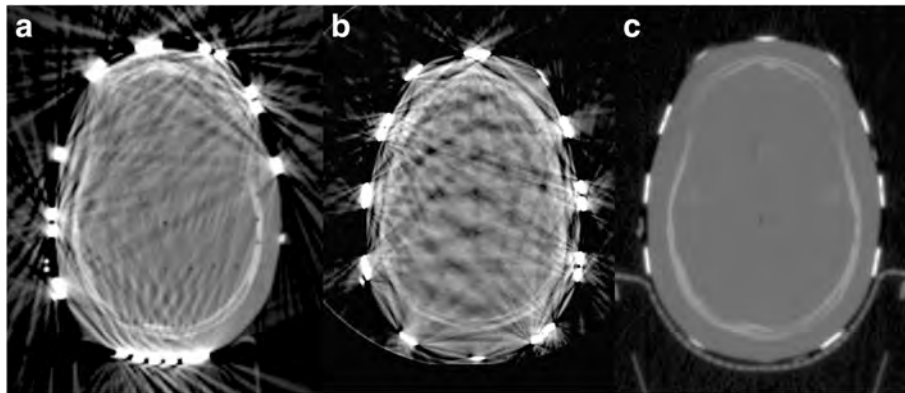
We used the AAA13 algorithm to calculate the dose distributions. This algorithm is based on electron densities which previously have to be converted from the HU

values of kV or MV-CTs. This is done by conversion tables that correlate HU values and electron densities [16]. The conversion tables are derived from scans of different materials with known electron densities and are machine-specific. We use distinct conversion tables for MV-CT based dose calculations within our daily routine, especially when patients with hip-replacements have to be treated within the pelvic area.

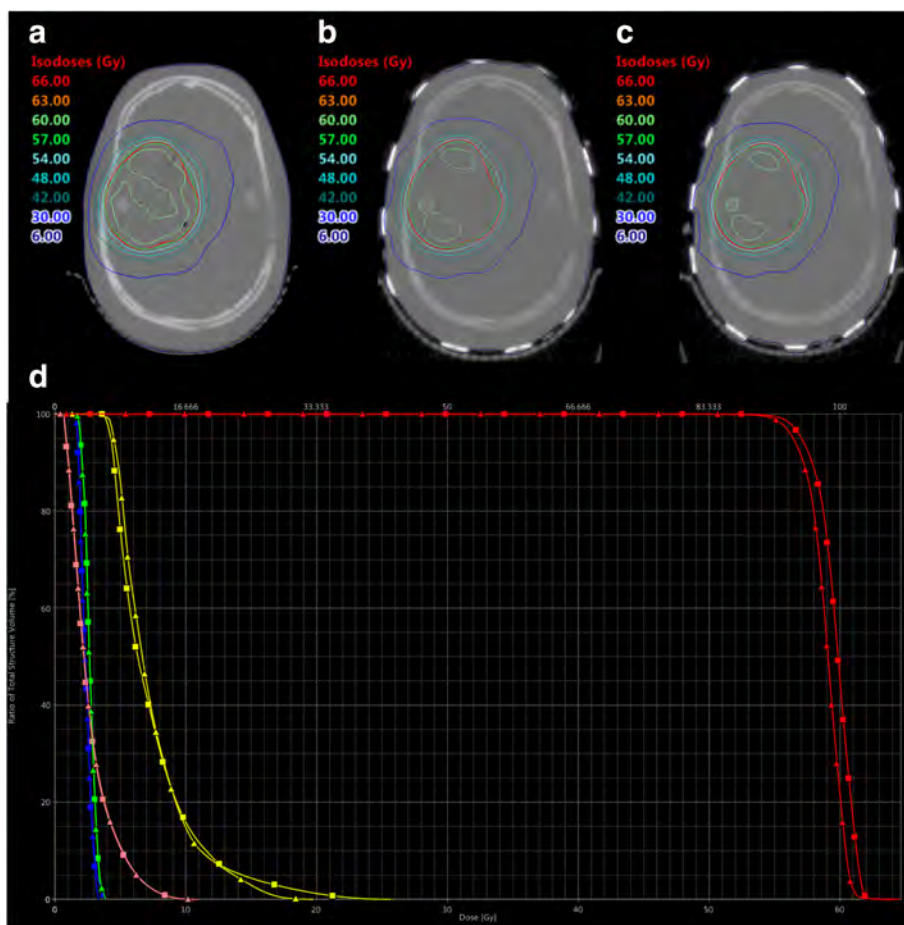
**Table 1** Comparison of the calculated to the measured doses in 2, 3 and 4 cm depth of a RW3 slab phantom. All experiments were performed with a Trilogy linear accelerator irradiating a 6 MV,  $15 \times 15$  cm<sup>2</sup> field with 200 MU. The doses were measured on 71 points directly below the TTField arrays with a MapCheck2 2D diode detector array. The arithmetic average as well as the standard deviation of the doses at these 71 measure points are presented

	depth	Without TTField arrays		With TTField arrays		Attenuation
		Average (cGy)	StdDev	Average (cGy)	StdDev	
kV	2 cm	214.3	1.10	199.1	4.90	7.09%
	3 cm	204.6	0.80	187.9	4.90	8.16%
	4 cm	194.3	0.60	177.6	4.70	8.59%
MV	2 cm	214.4	0.80	211.9	1.20	1.17%
	3 cm	204.6	0.60	199.5	1.20	2.49%
	4 cm	194.8	0.50	189.9	1.20	2.52%
Phantom	2 cm	214.6	1.60	207.4	4.00	3.36%
	3 cm	204.9	1.30	197.3	3.40	3.71%
	4 cm	195.0	1.10	189.8	4.20	2.67%



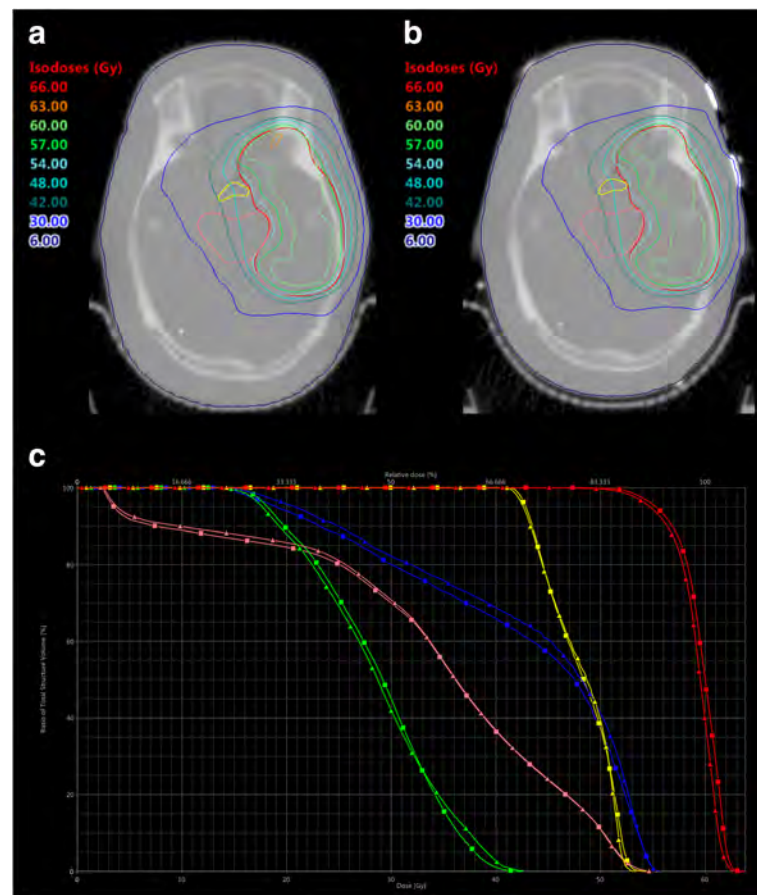


**Fig. 2** kV-CT (a), CBCT (b) and MV-CT (c) of an Alderson head phantom equipped with TTField transducer arrays (Range – 1000 to 3071 HU). In kV-CT and CBCT, bony structures are only visible when they are not within the direct vicinity of TTField arrays and streaky artefacts are present. In contrast, MV-CT is almost free of artefacts, all bony structures are clearly visible and also structures with a low radiographic density, i.e. bore holes, are resolved.



**Fig. 3** MV-CTs of an Alderson head phantom without (a) and with TTField arrays in position A (b) and B (c). A treatment volume resembling the PTV for a parietal glioblastoma was optimized to the MV-CT in (a) and re-calculated to MV-CT (b) and (c). (d) shows a DVH-comparison between the plan for (a) (squares) and (b) (triangles). Red: PTV, yellow: chiasm, blue: left optical nerve, green: right optical nerve, pink: brainstem





**Fig. 4** MV-CTs of an Alderson head phantom without (a) and with TTField arrays (b). A treatment plan for a target volume resembling the PTV for a temporopolar glioblastoma was optimized on the MV-CT in (a) and re-calculated to MV-CT (b). c shows a DVH-comparison between the plan for (a) (squares) and (b) (triangles). Red: PTV, yellow: chiasm, blue: left optical nerve, green: right optical nerve, pink: brainstem

The presence of high density materials, such as TTField arrays with a physical density of  $7.75 \text{ g/cm}^3$ , can lead to photon starvation that propagate to streak artefacts [17]. These artefacts are consequently represented by apparently high, in most cases maximum, HU values. In our case, the arrays as well as parts of the halo were represented by up to 3071 HU with kV-CT, corresponding to a relative electron density of 2.52. This value is lower than expected from the physical density, however, the true ED of the arrays is unknown. Furthermore, due to the artefacts, the thickness of the arrays is seemingly bigger (7 mm in kV-CT as compared to 2.5 mm of physical thickness). Altogether, artefacts in general and also in our special case lead to an impaired accuracy of the dose calculation [18]. This effect can be impressively seen in case of the kV-CT based dose calculation in Fig. 1a.

CT images that are based on higher energy photons, such as our MV-CTs with 3.5 MV, are less prone by artefacts. This is due to the energy dependence of different mechanisms of photon absorption, namely the photoelectric effect or the Compton effect. As a consequence,

scanning by a MV-CT results in an almost artefact free image - also in the presence of TTField arrays. A second aspect is the finding, that the allocated CT number of material with a high physical and electron density inversely correlates with the photon energy used for CT-scanning [19]. This leads to shallower ED-HU-conversion curve. The HU-value of the high density arrays is therefore still within the range of the HU table and not at its edge (2854 HU in parts of the arrays, representing a relative ED of 3.9). Based on these considerations we assumed that a MV-CT based dose calculation is more reliable in presence of TTField arrays than a dose calculation based on kV-CTs. The general applicability of MV-CTs for radiotherapy planning was already shown by other groups [20]. This assumption was further substantiated by measurements with a linear accelerator which showed a good accordance of the measurements with the calculations in terms of depth doses as well as with attenuations caused by the TTField arrays.

In principle, the accuracy of a kV-CT based dose calculation can theoretically be improved by extending



**Table 2** Dose distribution and conformity on PTV1, resembling a target volume for a parietal glioblastoma

PTV1	Optimized Plan	Re-Calculation on Position A	Re-Calculation on Position B
PTV			
D <sub>max</sub>	64.6 Gy	64.2 Gy	63.7 Gy
D <sub>2%</sub>	61.7 Gy	61.0 Gy	60.8 Gy
D <sub>mean</sub>	59.7 Gy	58.9 Gy	58.7 Gy
D <sub>50%</sub>	59.9 Gy	59.1 Gy	58.8 Gy
D <sub>98%</sub>	56.2 Gy	55.6 Gy	55.3 Gy
D <sub>min</sub>	50.2 Gy	45.8 Gy	47.2 Gy
Conformity (V <sub>95%</sub> /PTV)	0.93	0.89	0.87
Homogeneity ((D <sub>2%</sub> -D <sub>98%</sub> )/D <sub>50%</sub> )	0.09	0.09	0.09
Chiasm			
D <sub>max</sub>	25.7 Gy	19.8 Gy	20.7 Gy
D <sub>2%</sub>	18.4 Gy	15.6 Gy	16.3 Gy
D <sub>mean</sub>	7.4 Gy	7.4 Gy	7.7 Gy
V <sub>54Gy</sub>	0 cm <sup>3</sup>	0 cm <sup>3</sup>	0 cm <sup>3</sup>
V <sub>50Gy</sub>	0 cm <sup>3</sup>	0 cm <sup>3</sup>	0 cm <sup>3</sup>
Left Optical Nerve			
D <sub>max</sub>	3.4 Gy	3.8 Gy	3.8 Gy
D <sub>2%</sub>	3.2 Gy	3.5 Gy	3.6 Gy
D <sub>mean</sub>	2.3 Gy	2.4 Gy	2.4 Gy
V <sub>54Gy</sub>	0 cm <sup>3</sup>	0 cm <sup>3</sup>	0 cm <sup>3</sup>
V <sub>50Gy</sub>	0 cm <sup>3</sup>	0 cm <sup>3</sup>	0 cm <sup>3</sup>
Right Optical Nerve			
D <sub>max</sub>	3.6 Gy	3.9 Gy	3.9 Gy
D <sub>2%</sub>	3.5 Gy	3.6 Gy	3.7 Gy
D <sub>mean</sub>	2.7 Gy	2.7 Gy	2.7 Gy
V <sub>54Gy</sub>	0 cm <sup>3</sup>	0 cm <sup>3</sup>	0 cm <sup>3</sup>
V <sub>50Gy</sub>	0 cm <sup>3</sup>	0 cm <sup>3</sup>	0 cm <sup>2</sup>
Brainstem			
D <sub>max</sub>	11.0 Gy	10.7 Gy	11.2 Gy
D <sub>2%</sub>	7.5 Gy	7.5 Gy	7.7 Gy
D <sub>mean</sub>	2.7 Gy	2.7 Gy	2.7 Gy
V <sub>54Gy</sub>	0 cm <sup>3</sup>	0 cm <sup>3</sup>	0 cm <sup>3</sup>
V <sub>50Gy</sub>	0 cm <sup>3</sup>	0 cm <sup>3</sup>	0 cm <sup>3</sup>

the HU-table or replacing the electrodes in the CT dataset by the true electron density – which unfortunately is unknown. However, image artefacts outside the electrodes must also be corrected by the real tissue density and a replacement with one density might be insufficient, too. In addition, finding the correct position of the electrodes can be hampered by the artefacts. In contrast to this approach, MV-CT based dose calculation is free of additional corrections.

Based on these considerations, we investigated the impact of TTField arrays on the MV-CT based calculated dose delivery in two hypothetical cases of glioblastoma.

Comparison of the plans for two exemplary target volumes showed only minor effects on the plan quality. The homogeneity index was not affected when the TTField arrays were added to the setup and the conformity index showed only minor differences. Therefore, radiotherapy with simultaneously applied TTField arrays seems to be possible without negatively affecting the tumor control probability as similar doses are delivered independently from the presence of the arrays. Importantly, to our knowledge, there are currently no data available about possible synergistic effects between TTFields and radiation onto normal tissues.



**Table 3** Dose distribution and conformity on PTV2, resembling a target volume for a temporopolar glioblastoma

PTV2	Optimized Plan	Re-Calculation on Position A	Re-Calculation on Position B
PTV			
D <sub>max</sub>	63.8 Gy	63.8 Gy	63.3 Gy
D <sub>2%</sub>	62.4 Gy	62.1 Gy	61.9 Gy
D <sub>mean</sub>	59.6 Gy	59.1 Gy	59.0 Gy
D <sub>50%</sub>	60.0 Gy	59.5 Gy	59.4 Gy
D <sub>98%</sub>	53.5 Gy	52.9 Gy	53.1 Gy
D <sub>min</sub>	45.4 Gy	42.4 Gy	45.9 Gy
Conformity (V <sub>95%</sub> /PTV)	0.89	0.86	0.86
Homogeneity ((D <sub>2%</sub> -D <sub>98%</sub> )/D <sub>50%</sub> )	0.15	0.15	0.15
Chiasm			
D <sub>max</sub>	54.5 Gy	53.5 Gy	53.3 Gy
D <sub>2%</sub>	52.7 Gy	52.3 Gy	52.4 Gy
D <sub>mean</sub>	48.0 Gy	48.0 Gy	47.6 Gy
V <sub>54Gy</sub>	< 0.01 cm <sup>3</sup>	0 cm <sup>3</sup>	0 cm <sup>3</sup>
V <sub>50Gy</sub>	0.29 cm <sup>3</sup>	0.27 cm <sup>3</sup>	0.24 cm <sup>3</sup>
Left Optical Nerve			
D <sub>max</sub>	55.5 Gy	55.7 Gy	55.4 Gy
D <sub>2%</sub>	54.7 Gy	54.7 Gy	54.6 Gy
D <sub>mean</sub>	42.3 Gy	43.3 Gy	41.7 Gy
V <sub>54Gy</sub>	0.02 cm <sup>3</sup>	0.02 cm <sup>3</sup>	0.02 cm <sup>3</sup>
V <sub>50Gy</sub>	0.11 cm <sup>3</sup>	0.12 cm <sup>3</sup>	0.13 cm <sup>3</sup>
Right Optical Nerve			
D <sub>max</sub>	42.6 Gy	42.7 Gy	43.0 Gy
D <sub>2%</sub>	39.3 Gy	40.4 Gy	39.9 Gy
D <sub>mean</sub>	28.6 Gy	28.5 Gy	27.4 Gy
V <sub>54Gy</sub>	0 cm <sup>3</sup>	0 cm <sup>3</sup>	0 cm <sup>3</sup>
V <sub>50Gy</sub>	0 cm <sup>3</sup>	0 cm <sup>3</sup>	0 cm <sup>3</sup>
Brainstem			
D <sub>max</sub>	55.5 Gy	55.7 Gy	55.1 Gy
D <sub>2%</sub>	52.7 Gy	52.6 Gy	52.2 Gy
D <sub>mean</sub>	33.9 Gy	34.3 Gy	33.7 Gy
V <sub>54Gy</sub>	0.09 cm <sup>3</sup>	0.10 cm <sup>3</sup>	0.02 cm <sup>3</sup>
V <sub>50Gy</sub>	2.82 cm <sup>3</sup>	2.78 cm <sup>3</sup>	2.48 cm <sup>3</sup>

The doses at deeply seated OARs, such as the chiasm, the optic nerves or the brainstem, were also not increased by more than 0.4 Gy by the presence of the arrays. This is within the range of the inherent dose calculation uncertainties of current treatment planning systems and largely below uncertainties due to positioning errors [21, 22]. However, even a small increase in the D<sub>max</sub> could have detrimental late effects, the dose constraints should be chosen conservatively and met exactly, especially as additional biologic TTField effects on normal tissues are unknown. In summary, based on the criteria of ICRU report 83, the absorbed doses within the PTV as well as

the OAR are affected by the presence of TTField arrays, but the differences are not likely to be of clinical relevance [15]. Or with other words: if an increased rate of adverse events would be observed during concomitant use of TTFields and radiotherapy, with TTField arrays attached during irradiation, then this likely would not be due to a change within the dose delivery but to an additional biologic effects.

Besides only modest effects on the dose-distribution within the depth, a bolus effect caused by the electrodes was shown by us as well as by Bender et al. [14]. Notably, the bolus effect to the skin was not the main focus



of this manuscript and was therefore calculated only for static 0° fields. The overdosing within the skin can still be relevant, but as the positions of the arrays are changed every 3 days, potential side effects, mostly to the skin, can be attenuated. However, since hair loss is present depending on the size and the location of the lesion of the GBM, such overdosing at the skin and hair level might increase the rate of permanent alopecia and should be kept in mind when counselling the patients.

Additionally, daily repositioning can be performed precisely even with the TTField system present during the treatment process, especially when MV-CT can be used for positioning. As the OAR of the CNS are mostly located at the skull base, and as this area is usually not covered by the TTField arrays, sufficient registration of the skull base is also possible with kV-CT or CBCT, too. When soft tissue information is deemed to be important for repositioning, MV-CT based imaging or daily change of the TTField arrays can be performed.

Notably, the biology effects of TTFields and potential additive effects with radiation have only been studied in cell lines of malignant tumors so far and no preclinical evidence about the effect of a concomitant application of TTFields and RT on normal tissue exist. There is a potential risk, that a combination of the two modalities might also increase the risk of side effects. For instance, a reduced fractionation effect could be assumed based on a delayed repair of radiation induced DNA damages, even though this was only shown for malignant cells [8]. This potentially could also lead to an increase in severe late effects, such as radionecrosis. On the other hand, as there is only limited proliferative activity within healthy adult brain tissue and no severe neurotoxicity after TTField-treatment has been reported so far, one could also assume a relatively low risk for an excessive increase in normal tissue side effects by combining these two modalities. Therefore, further preclinical studies on the impact of this modality in normal tissue radiation tolerance as well as treatment within clinical trials are highly recommended before the routine use of concomitant radio-TTField-treatments.

## Conclusion

Electrode arrays of the Optune TTField-system cause streak artefacts on kV-CTs which are impairing trustworthy dose calculations. Our data show that application of the TTField arrays during treatment planning and application of RT does not impact dose calculations, if the dose is calculated based on a MV-CT dataset. Use of MV-CTs for optimizing VMAT plans as well as for recalculation of already optimized VMAT treatment plans reveal only minor effects of TTField arrays on the conformity, homogeneity and median dose as well as the doses at OARs. Noteworthy, an increased skin toxicity

seems to be likely. As the area above the skull base is broadly spared by the TTField arrays and consequently is only slightly effected by artefacts, repositioning can be safely performed also with CBCTs. Based on these findings, irradiation of VMAT plans optimized without the presence of TTField arrays seems to be feasible, yet a possible adverse synergistic interaction of TTFields and radiation onto normal tissues should be considered, too.

## Additional file

**Additional file 1: Figure S1:** Example of TTField arrays attached to an Alderson head phantom. (PNG 25896 kb)

## Abbreviations

AAA: Anisotropic analytical algorithm; CBCT: Cone beam computed tomography; CT: Computed tomography; FDA: Food and drug association; GBM: Glioblastoma; GTR: Gross total resection; GTV: Gross tumor volume; HU: Hounsfield units; ICRU: International commission on radiation units; kV-CT: Kilo voltage computed tomography; MU: Monitor units; MV-CT: Mega voltage computed tomography; NCCN: National comprehensive cancer network; OAR: Organ at risk; PTV: Planning target volume; RT: Radiotherapy; SD: Standard deviation; TTField: Tumor treatment fields; VMAT: Volumetric arc therapy

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## Availability of data and materials

All experimental data are available upon request.

## Authors' contributions

CS designed the study, generated the target volumes, analysed the data and prepared the manuscript. MO and SK did the measurements, optimized the treatment plans and gave important intellectual input for planning the experiments. SS and FSG thoroughly revised the manuscript and gave intellectual input. JW and SEC supervised the work and revised the manuscript. All authors approved the final version for submission.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Competing interests

CS: received a Scholarship from Medac GmbH, received travel Grant from NovoCure; MO, SK, SS, JW: No conflict of interest. FSG: served as author for Medac GmbH; SEC: Advisory board of Bristol-Myers Squibb, Advisor for BrainLab, Author for Medac GmbH. The remaining authors declare to have no conflict of interest do declare.

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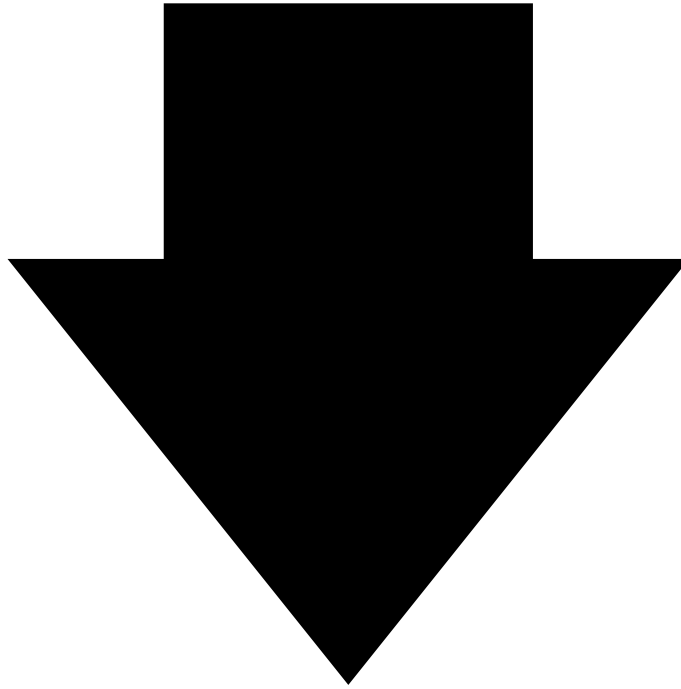
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PRACTICE CHANGING

January , ....

## Electrical Field Therapy for Glioblastoma

*Roy E. Strowd, MD reviewing Stupp R et al. JAMA 2017 Dec 19*

Case 1:20-cv-00194-WCG Filed 04/28/20 Page 139 of 1212 Document 11-2 1618





*Adding tumor-treating electrical-field therapy to maintenance temozolomide chemotherapy significantly improved survival in patients with newly diagnosed glioblastoma.*

Tumor-treating fields (TTFields) are a new electrical-field therapy being used to target mitotically active tumor cells, arrest growth, and induce apoptosis in patients with glioblastoma. TTFields are delivered continuously by a transducer array, which is similar to an electroencephalography electrode cap and is worn on a shaved scalp.

A prior planned interim analysis of an industry-funded, multicenter, open-label, randomized, phase III study (EF-14) showed that adding TTFields to maintenance temozolomide chemotherapy significantly prolonged survival in 315 patients with newly diagnosed glioblastoma ([NEJM JW Neurol Feb 2015](#) and [JAMA 2015; 314:2535](#)). Investigators now report final results of the EF-14 study, which includes 695 patients who received TTFields for a median 8.2 months (range, 0–82 months) and were followed for a median of 40 months.

Median progression-free survival (the primary endpoint) was improved with TTFields plus temozolomide versus temozolomide alone (6.7 vs. 4.0 months;  $P < 0.001$ ). Median overall survival (OS) was also improved with the addition of TTFields (20.9 vs. 16.0 months;  $P < 0.001$ ), equating to 18% more patients alive at 1 year, 10% more alive at 3 years, and 8% more alive at 5 years. The benefit of TTFields was observed in all major subgroups. Among the TTFields group, OS was longer for patients who used TTFields for  $\geq 18$  versus  $< 18$  hours per day (22.6 vs. 19.2 months;  $P = 0.009$ ).

## COMMENT

Although this trial lacked a sham intervention, studies without placebo control have changed clinical practice in neuro-oncology, including the registration trial for temozolomide, which was approved without placebo control and is widely used ([N Engl J Med 2005; 352:987](#)). The current study, which incorporated intention-to-treat analysis, central radiology review, and robust molecular characterization, shows a survival advantage and an apparent dose-response. In addition, this therapy is well tolerated by patients, and increased seizure risk has not proven to be an issue. As with new therapies, TTFields continue to be adopted variably in practice. With the publication of these results, clinicians will increasingly care for patients using TTFields.

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## CITATION(S):

Stupp R et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: A randomized clinical trial. *JAMA* 2017 Dec 19; 318:2306. <https://doi.org/10.1001/jama.2017.18704>

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Regarding the randomization, women were randomized by a web-based system (<http://www.randomization.com>) using random blocks of 2, 4, and 6 to receive the pessary or no pessary. Randomization was stratified by cervical length, and separate randomization sequences were created by an independent statistician. However, there was an error in the article. The randomization strata were less than 20 mm and equal or greater than 20 mm to equal or less than 25 mm, not equal or less than 20 mm and greater than 20 mm to equal or less than 25 mm as stated. Using the erroneous cutoff would lead to imbalance between the groups, as Thornton suggested. However, with the correct cutoff, no imbalance was noticed, with 125 women with a cervical length less than 20 mm and 25 women with a cervical length equal or greater than 20 mm to equal or less than 25 mm in each group. The number of women with a cervical length equal or less than 20 mm in Table 1 was correct, as equal or less than 20 mm was the cutoff used for vaginal progesterone therapy, as recommended by guidelines.<sup>2</sup> The article has been corrected online and we apologize for any confusion this may have caused.

Regarding the Kaplan-Meier curves, the numbers of women at risk, reported in Figure 2, were the total number of randomized women minus the number of women who already delivered, regardless of whether they had iatrogenic or spontaneous preterm birth. Therefore, the numbers of women at risk are the same for both curves.

The benefits of the pessary shown in our trial could be explained by the high treatment adherence compared with other trials. There are several ongoing trials evaluating the efficacy of cervical pessary in prevention of preterm birth, and there are plans for an individual patient data meta-analysis that will include our data. The meta-analysis will update prior reviews<sup>3,4</sup> and hopefully will clarify the effect of cervical pessary in prevention of preterm birth.

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**Conflict of Interest Disclosures:** Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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## Quality of Life in Patients With Glioblastoma Treated With Tumor-Treating Fields

**To the Editor** In a multisite, randomized, phase 3, clinical trial, Dr Stupp and colleagues<sup>1</sup> demonstrated a modest benefit for patients newly diagnosed with glioblastoma treated with tumor-treating fields (TTFields) and temozolomide vs temozolomide alone in progression-free survival (7.1 months for TTFields plus temozolomide vs 4 months for temozolomide alone) and overall survival (20.9 months for TTFields plus temozolomide vs 16 months for temozolomide alone). The authors should justify the current cost of the device (\$20 000 per month) and also discuss the effect on quality of life for both the patients (shaving their head) and family when patients wear the TTFields device 18 hours a day.

Cognitive (Mini-Mental State Examination) and functional (Karnofsky performance score) metrics were included in their analysis, but the use of standardized, health-related quality-of-life scores (such as the European Organisation for Research and Treatment of Cancer quality-of-life questionnaire and its brain-specific module) were not mentioned. Tumor-treating fields plus temozolomide compared with temozolomide alone showed no significant differences in time to a sustained 6-point decline in the Mini-Mental State Examination score.<sup>1</sup> Standardized health-related quality-of-life scores take into account emotional, social, and role functioning.<sup>2</sup> An interim analysis conducted on the first 315 randomized patients did not show significant differences for any of the functional scales on either questionnaire in either treatment group.<sup>2</sup> A larger analysis incorporating 92% of the patients noted that 42% of patients had not completed the questionnaires at the 1-year follow-up.<sup>3</sup> The physical and emotional burden of shaving one's head while wearing the device 18 hours a day (including while sleeping) cannot be underestimated for both patient and family members. In fact, it is the partner, friend, or family member who must change the adhesives, administer scalp care, and adjust the TTFields device when it malfunctions, even in the middle of the night.

Other trials, perhaps with less significant psychiatric implications, may be better suited for patients with newly diagnosed glioblastoma. For example, a phase 3 trial (CeTeg/NOA-09) showed that the combination of lomustine and temozolomide significantly improved median overall survival (37.9 months with lomustine, temozolomide, and radiotherapy vs 31.4 months with temozolomide and radiotherapy alone) in patients with the O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT) promoter.<sup>4</sup>

In sum, although TTFields plus temozolomide provides an interesting and innovative treatment for newly diagnosed glioblastoma, a better understanding of the effect on patient and family quality of life needs to be assessed, especially to justify TTFields's increased economic and emotional burden.

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**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma. *JAMA*. 2017;318(23):2306-2316.
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**In Reply** Our randomized trial demonstrated a consistent improvement in both progression-free and overall survival when TTFields was included in first-line therapy for glioblastoma. The hazard ratio for death was 0.63, translating into an improvement in the 2-year survival rate from 31% to 43%. For comparison, the addition of temozolomide to radiotherapy compared with radiotherapy alone also resulted in a hazard ratio of 0.63, with a 2-year survival rate increasing from 10% to 27%.<sup>1</sup> One may consider the improvements modest, yet these are the most effective proven treatments available.

Cancer treatments, be it surgery, irradiation, chemotherapy, or TTFields, all have their inherent toxicities and inconveniences. The results of the health-related quality-of-life analyses that Dr Kwan and colleagues requested have recently been published in detail.<sup>2</sup> The main adverse effect of TTFields was skin reactions (mostly mild) at the site of electrode placement. We hypothesized that wearing the device could either decrease health-related quality of life through its burden on the patient, including physical impairment or a decreased social or role functioning due to the visibility of the device, or increase it through an improved feeling of well-being related to active participation of both the patient and the caregiver in the fight against the disease. Instead, no statistically significant differences in health-related quality of life between baseline and 12 months were observed between groups, except for itchy skin in the TTFields group. Health-related quality-of-life scores were maintained for a longer period in the TTFields group due to the longer time to tumor progression and survival. Missing longitudinal quality-of-life data are an inherent problem of many studies as is overrepresentation of patients with favorable prognostic factors. However, our mixed-model analyses, accounting for missing data, confirmed the results found in the mean change from baseline analyses.

Kwan and colleagues point out that there may be other treatments that could confer a benefit in outcome. We embrace any future advances made in the treatment of patients with malignant glioma. The TTFields treatment has no overlapping toxicities and thus could be combined with any other

promising therapy; TTFields treatment is an important step toward improvement in survival, but further research is needed to ultimately cure patients with glioblastoma.

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**Conflict of Interest Disclosures:** Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Stupp reported fees paid to his institution from and serving on advisory boards of Celgene, Novartis, AbbVie, and Merck KGaA (Darmstadt) and travel support from Novocure and that his spouse works full time for Novartis. Dr Ram reported that he has received grants, personal fees, stock, and nonfinancial support from Novocure.

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987-996.
2. Taphoorn MJB, Dirven L, Kanner AA, et al. Influence of treatment with tumor-treating fields on health-related quality of life of patients with newly diagnosed glioblastoma [published online February 1, 2018]. *JAMA Oncol*.

## The National Resident Matching Program and Competition for Employment

**To the Editor** Dr Curtin and Ms Signer<sup>1</sup> advocated for the policies of the National Resident Matching Program (NRMP) to maintain “a fair, efficient, and reliable matching process.” However, we believe this article minimizes the inherent inequity of the NRMP binding match commitment, which requires medical students to enter the Match contractually obligated to an employment agreement they have never seen. Matched applicants are then not allowed any negotiation of the employment agreement that they were bound to sign. Rigorous enforcement of these contracts are justified by Curtin and Signer to ensure the “integrity” of the process, which is the only means of securing residency positions in the United States.

The contractual obligation of resident physicians to the NRMP fundamentally violates antitrust laws by undermining competition in recruitment and hiring, thereby lessening employment choice and compensation. In the face of a court challenge to the NRMP, the process has been protected from legal scrutiny by Congress. This was accomplished through an exemption of the NRMP in an amendment to the unrelated Pension Fund Equity Act of 2004. The amendment, which had not undergone hearings before appropriate committees, retroactively and permanently exempted graduate medical education programs from antitrust law.

We agree that the NRMP is efficient and effective; in fact, the 2012 Nobel Prize in Economics was awarded for the algorithm on which the NRMP is based.<sup>2</sup> However, the Congressional exemption of the NRMP from antitrust laws and the secretive means by which it was enacted were not proper. The amendment to the Pension Fund Equity Act of 2004 was not procompetitive, as it prevents fair negotiations at the heart of all employment agreements.<sup>3</sup>



## Development of a Method for Improving the Electric Field Distribution in Patients Undergoing Tumor-Treating Fields Therapy

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Tumor-treating fields therapy involves placing pads onto the patient's skin to create a low-intensity (1 - 3 V/cm), intermediate frequency (100 - 300 kHz), alternating electric field to treat cancerous tumors. This new treatment modality has been approved by the Food and Drug Administration in the USA to treat patients with both newly diagnosed and recurrent glioblastoma. To deliver the prescribed electric field intensity to the tumor while minimizing exposure of organs at risk, we developed an optimization method for the electric field distribution in the body and compared the electric field distribution in the body before and after application of this optimization algorithm. To determine the electric field distribution in the body before optimization, we applied the same electric potential to all pairs of electric pads located on opposite sides of models. We subsequently adjusted the intensity of the electric field to each pair of pads to optimize the electric field distribution in the body, resulting in the prescribed electric field intensity to the tumor while minimizing electric fields at organs at risk. A comparison of the electric field distribution within the body before and after optimization showed that application of the optimization algorithm delivered a therapeutically effective electric field to the tumor while minimizing the average and the maximum field strength applied to organs at risk. Use of this optimization algorithm when planning tumor-treating fields therapy should maintain or increase the intensity of the electric field applied to the tumor while minimizing the intensity of the electric field applied to organs at risk. This would enhance the effectiveness of tumor-treating fields therapy while reducing dangerous side effects.

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Keywords: Tumor-treating fields, Alternating electric field, Optimization algorithm, Cancer therapy, Electric field calculation

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### I. INTRODUCTION

Tumor-treating fields (TTFields) therapy is a novel antimitotic cancer treatment modality that disrupts cancer cell replication by applying alternating electric fields of low intensity (1 - 3 V/cm) and intermediate frequency (100 - 300 kHz) [1,2]. Because its efficacy in treating patients with recurrent glioblastoma (GBM) was comparable to that of chemotherapy, but with fewer side effects, TTFields therapy was approved by the U.S. Food and Drug Administration (FDA) in 2011 to treat patients with recurrent GBM. TTFields therapy in combination with chemotherapy was shown to enhance survival compared with chemotherapy alone in patients with newly diagnosed GBM, resulting in its approval by the FDA in 2015 for this indication [3-6]. At present, only six

years after its initial approval by the U.S. FDA, TTFields therapy is being performed to treat GBM in about 950 treatment centers worldwide. Moreover, clinical trials have reported that TTFields therapy is 1.5 - 2.5 times more effective than conventional treatments in patients with lung, pancreatic and ovarian cancer, and it is being evaluated in other types of cancer [7-12].

Efforts are also underway to maximize the therapeutic effects of TTFields therapy. A previous study showed that the force exerted on a microscopic polarizable organelle in the cell is proportional to the square of the electric field, *i.e.*, the electric field intensity [13]. As a result, increases in the electric field intensity have been found to result in greater blockage of cancer cell division and induction of cell death in various cancer cell lines [13-16]. Specific frequency ranges have shown maximum effectiveness at blocking cancer cell division, even at the same electric field intensity [2, 13, 15]. Electric fields of about 200 kHz have shown the maximum effect

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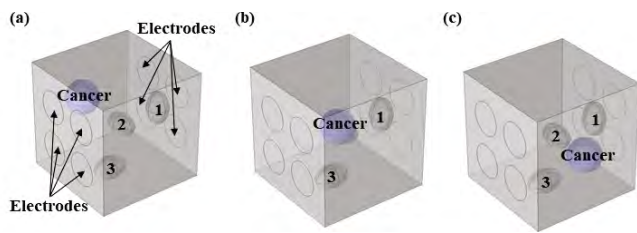


Fig. 1. (Color online) Simple Model Structure.

in treating patients with GBM, and the TTFields treatment planning system, NovoTAL software, determines the size and the position of the tumor relative to each patient's individual anatomy and selects the position of the electric pads to maximize the field strength at the tumor during treatment [17–19].

Although TTFields treatment is a promising modality to treat patients with various types of cancers, it has the potential for long-term side effects. It is, therefore, important to study methods that increase the intensity of electric fields applied to tumors, thereby enhancing its therapeutic effects, while minimizing exposure of organs at risk (OARs). Few studies, however, have assessed methods for optimizing the intensities of electric field [20,21]. Optimization algorithms that control the amount of radiation administered are frequently used for patients undergoing conventional radiation therapy [22–24]. These algorithms are based on determinations of the prescribed dose to be applied to the tumor and the allowable dose to OARs that does not cause side effects. This method can more easily control radiation dose to the body than methods in which several conditions (*e.g.*, the amount, direction, and intensity of radiation) are repeatedly changed, requiring re-calculation of radiation doses delivered to the body [25–27].

Similar to planning methods for radiotherapy, we used an optimization algorithm to optimize the electric field distribution in the body, allowing the application of electric fields with the prescribed intensities to tumors while minimizing the intensities of electric fields at OARs. The distributions of the electric fields in the body were compared using this method and existing treatment approaches that do not use optimization algorithms.

## II. EXPERIMENTS

### 1. Design of model

This research was performed using simple self-made models and models based on actual patients' computed tomography (CT) dicom files. The simple model consisted of an 8000-cm<sup>3</sup> cube containing three ovals, each 50.1 cm<sup>3</sup> in volume but at different positions, as well as one 112.5 cm<sup>3</sup> sphere; these represented OARs 1, 2, and 3 and the tumor, respectively (Fig. 1). Three types of

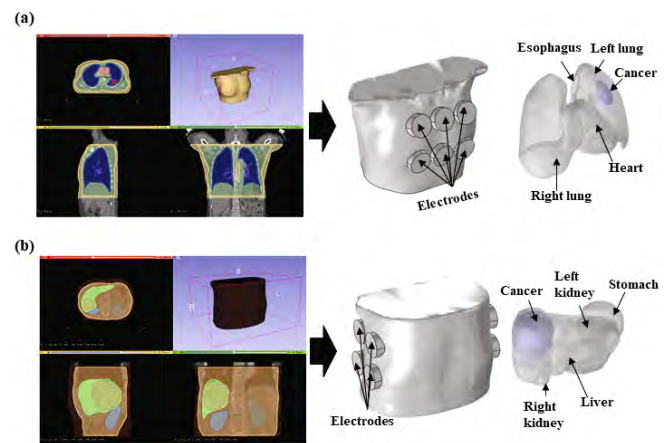


Fig. 2. (Color online) Interior and exterior of the patient model created based on CT data for patients with (a) lung and (b) liver cancer.

models were constructed, differing only in the position of the tumor, which was at the top (Fig. 1(a)), center (Fig. 1(b)), or bottom (Fig. 1(c)) of the cube. The area of each electrode that transmit the electric field to the model was 28.3 cm<sup>2</sup>. Four electrodes are attached to each of the two opposite sides of the cube, with a 2-cm gap between electrodes.

Patient models were based on the CT dicom files of actual patients with lung and liver cancer. In the lung cancer model, OARs, such as the lungs, esophagus, and heart, were segmented based on CT images, and the tumor was drawn on the CT images. In the liver cancer model, OARs, such as the stomach and kidneys, as well as the tumors, were segmented based on CT images. Volume meshes were made via simpleware software (Synopsis, USA) and were transferred to COMSOL Multiphysics software (COMSOL, USA). The lung cancer model included six electrodes, of around 28.5 cm<sup>2</sup>, placed in the area of each of the two opposite skin surfaces whereas the liver cancer model included four electrodes, of around 30.6 cm<sup>2</sup>, in the area of each of the two opposite skin surfaces (Fig. 2).

### 2. Computation of electric fields

The electric fields formed within the models were calculated using the COMSOL AC/DC module, which performs a finite-element analysis of Maxwell's equations. In the simple models, the conductivity of all organs was set at 0.1 S/m, and the permittivity was set at 1000. In the patient models, the conductivity and the permittivity values at 200 kHz were set to values appropriate for each organ from the literature [20,28,29]. Electrodes on the two opposing sides were selected one by one so that all the electrodes on one side could be matched with those on the other side one by one. To calculate the electric



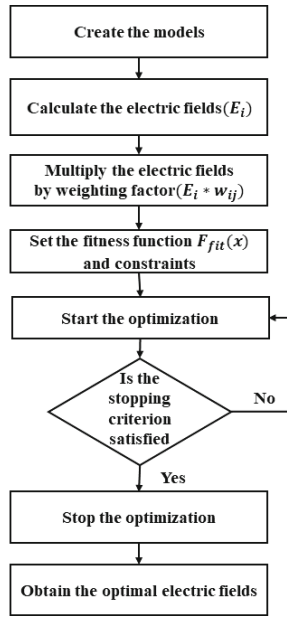


Fig. 3. Process for calculating the optimal electric field distribution through the optimization algorithm.

field, we set the alternating current (AC) voltage of one electrode was to 10–100 V<sub>pp</sub>, 200 kHz and the corresponding electrode at ground. That is, 16 ( $E_1 \sim E_{16}$ ) and 36 ( $E_1 \sim E_{36}$ ) electric field distributions were obtained for models with four and six electrodes on each side, respectively. These electric field distribution values ( $E_i$ ) were each multiplied by weighting factors ( $w_i$ ), and the final distribution ( $E_{\text{final}}$ ) was calculated by the combination of these distribution values, as in Eq. (1).

$$E_{\text{final}}(w_{ij}) = \frac{\sum_{i=1}^n w_{ij} * E_i}{\text{Number of electrodes used}}. \quad (1)$$

### 3. Optimization method

This research used a genetic algorithm (GA), a global optimization algorithm technique based on Darwin's concept of survival of the fittest [30,31]. A randomly created initial population is subjected to three processes (selection, crossover, and mutation) based on the resulting values of a calculated fitness function, to create a population that is more evolved than the initial population. The genetic processes are performed again based on this population's resulting values to create another population, and the process is repeated. When set conditions are met or a better fitness function cannot be obtained, the algorithm is considered to have found the optimal condition (Fig. 3) [31–33].

Equation (2) was set as the fitness function, and optimization was performed to adjust the weighting factors to obtain the minimum fitness function value ( $F_{\text{fit}}$ ). If  $E_{\text{ave1}}$ ,  $E_{\text{ave2}}$ , and  $E_{\text{ave3}}$  are the mean electric field values

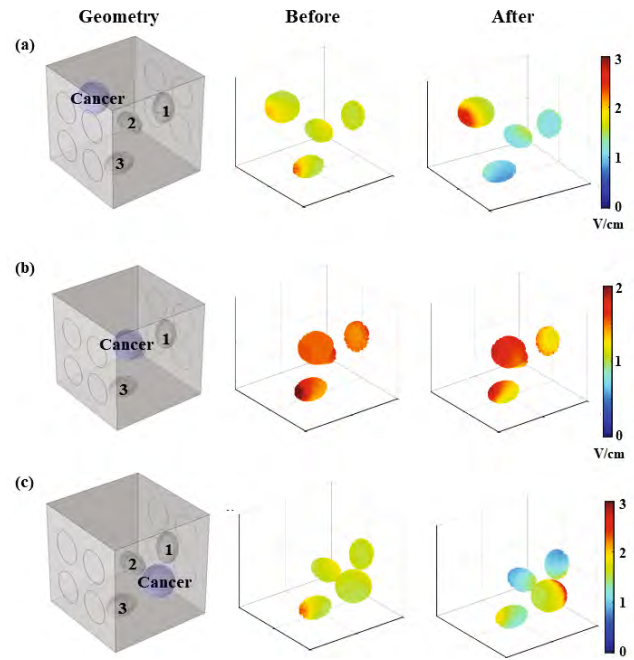


Fig. 4. (Color online) Interior electric-field distributions before and after application of the optimization algorithm for tumors located at the (a)top, (b)center, and (c)bottom of the cube.

transmitted to the OARs, and  $Std_{\text{cancer}}$  is the standard deviation of the electric field intensity transmitted to the tumor, then

$$F_{\text{fit}}(w_{ij}) = E_{\text{ave1}}(w_{ij}) + E_{\text{ave2}}(w_{ij}) + E_{\text{ave3}}(w_{ij}) + Std_{\text{cancer}}(w_{ij}). \quad (2)$$

Constraints were designed to deliver an electric field strength  $\geq 1.5$  V/cm to the tumor and less than the maximum field strength to the OARs when the same electric potential was applied to all electrodes.

### 4. Evaluation method

To evaluate the treatment planning method using the optimization algorithm, we determined the electric field distribution in the body resulting from the application of the same electric potential to all the electrodes on opposite sides. These findings were normalized to allow transmission of an electric field  $> 1.5$  V/cm to the entire volume of the tumor.

The two methods were evaluated by constructing a 3-D map representing the electric field intensity transmitted to the tumor and the OARs (Figs. 4 and 6) and by constructing a graph in which the horizontal axis represent the electric field intensity and the vertical axis represent the percentage of the total volume of a given tissue in which the magnitude of the electric field exceeded that



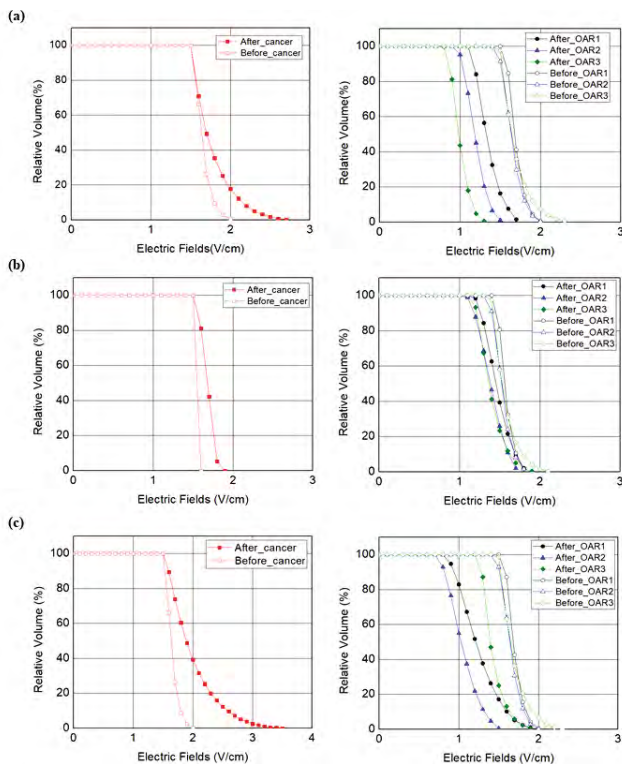


Fig. 5. (Color online) Percentage of the total volume of a given tissue in which the magnitude of the electric field exceeded that along the horizontal axis before and after application of the optimization algorithm for tumors located at the (a) top, (b) center, and (c) bottom of the cube.

in the horizontal axis in V/cm (Figs. 5 and 7), the maximum electric field intensity of the specific organ ( $E_{\max}$ ), the average electric field intensity of the specific organ ( $E_{\text{ave}}$ ), and the values ( $V_{30}$ ,  $V_{60}$ ,  $V_{90}$ ) of the relative volume which had 30% (= 0.45 V/cm), 60% (= 0.90 V/cm), or 90% (= 1.35 V/cm) of 1.5 V/cm transmitted. These factors are those used for evaluating radiation treatment plans [34,35].

### III. RESULTS AND DISCUSSION

#### 1. Simple models

Figure 4 shows 3-D graphs of the internal electric field distributions with (optimization method) and without (existing method) the optimization algorithm, enabling a qualitative determination of the electric field intensity transmitted to each internal organ. In all three models, there were more areas of application of  $\geq 2$  V/cm electric field intensity to the tumor than in the existing method, along with many areas of application of  $\leq 1$  V/cm electric-field intensity at the OARs. A comparison of the two methods in Fig. 4(a) showed that the

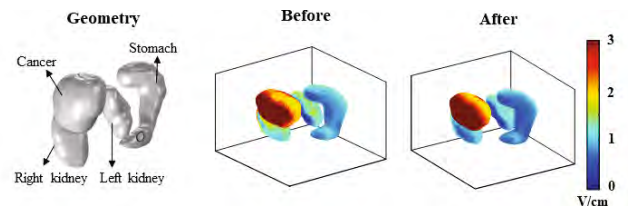


Fig. 6. (Color online) Distributions of internal electric fields in a liver cancer model before and after application of the optimization algorithm.

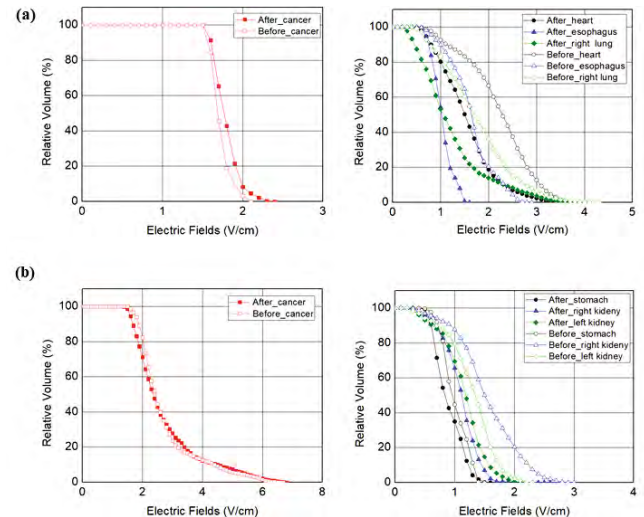


Fig. 7. (Color online) Percentage of the total volume of a given tissue in which the magnitude of the electric field exceeded that along the horizontal axis before and after application of the optimization algorithm in the (a) lung and (b) liver cancer models.

optimization method increased the area of the tumor exposed to  $\geq 2$  V/cm by more than half and reduced the intensity to most OARs from 1 - 1.5 V/cm to  $< 1$  V/cm. In Fig. 4(b), the optimization method increased the intensity to most of the tumor to  $\geq 2$  V/cm and altered the intensity to most OARs from 1.5 - 2 V/cm to around 1 V/cm. In Fig. 4(c), the optimization method increased the area of the tumor exposed to 2 V/cm by around half and reduced exposure of about half of the OARs from 1.5 - 2 V/cm to  $< 1$  V/cm. Also, regardless of whether the existing method or the optimization method was used, the electric fields were greater in some parts of the tumor than in other parts and were greater for OARs near the surface than for OARs at deeper locations. This was likely due to the greater electric field intensity in areas close to, rather than more removed from, an electrode, thereby increasing exposure of organs near surface electrodes.

The treatment plan was designed so that the entire volume was exposed to an electric field  $\geq 1.5$  V/cm (Fig. 5). The maximum electric-field intensity transmitted to the tumor was larger after than before using the optimization algorithm (2.77 V/cm vs. 2.40 V/cm, respectively,



Table 1. Comparisons of the  $V_{30}$ ,  $V_{60}$ ,  $V_{90}$ ,  $E_{\max}$ , and  $E_{\text{ave}}$  values for each OAR for tumors at the (a) top, (b) center, and (c) bottom of the cube.

(a)	Organ 1			Organ 2			Organ 3		
	BO	AO	Difference	BO	AO	Difference	BO	AO	Difference
$V_{30}$	100	100	0	100	100	0	100	100	0
$V_{60}$	100	100	0	100	100	0	100	81	19
$V_{90}$	100	44	56	100	13	87	100	0	100
$E_{\max}$	2.02	1.78	0.24	2.02	1.53	0.49	2.40	1.34	1.06
$E_{\text{ave}}$	1.70	1.35	0.35	1.65	1.19	0.46	1.69	1.00	0.69
(b)	Organ 1			Organ 2			Organ 3		
	BO	AO	Difference	BO	AO	Difference	BO	AO	Difference
$V_{30}$	100	100	0	100	100	0	100	100	0
$V_{60}$	100	100	0	100	100	0	100	100	0
$V_{90}$	100	74	26	99	58	41	100	53	47
$E_{\max}$	1.88	1.87	0.01	1.88	1.78	0.10	2.19	1.93	0.26
$E_{\text{ave}}$	1.58	1.47	0.11	1.53	1.39	0.14	1.57	1.39	0.18
(c)	Organ 1			Organ 2			Organ 3		
	BO	AO	Difference	BO	AO	Difference	BO	AO	Difference
$V_{30}$	100	100	0	100	100	0	100	100	0
$V_{60}$	100	95	5	100	77	23	100	100	0
$V_{90}$	100	32	68	100	8	92	100	67	33
$E_{\max}$	2.03	2.03	0.00	2.02	1.59	0.43	2.36	1.96	0.40
$E_{\text{ave}}$	1.70	1.25	0.45	1.65	1.05	0.60	1.69	1.43	0.26

Abbreviations: BO, before application of the optimization algorithm; AO, after application of the optimization algorithm.

in Fig. 5(a); 1.88 V/cm vs. 1.55 V/cm, respectively, in Fig. 5(b); and 3.54 V/cm vs. 2.05 V/cm, respectively, in Fig. 5(c)). The optimization method resulted in the transmission of 0.33 - 1.49 V/cm greater intensity. These findings confirmed that the optimization algorithm made possible the application of a greater electric field to the tumor than the existing method.

In assessing OAR graphs (Fig. 5), we found that all the graphs for the optimization method were positioned to the left ( $y$ -axis) of the graphs for the existing method, with the optimization method having a similar or lower maximum electric-field intensity. Quantitative analyses also showed that the maximum electric-field intensity was equal or lower using the optimization than the existing method in all three organs at risk in all three models (*i.e.* nine conditions), with differences of 0.00 - 1.06 V/cm (Table 1). The average electric-field intensity was also lower in all nine conditions, with differences of 0.11 - 0.69 V/cm. Comparing the electric-field intensity doses in sections showed that the relative volumes of OARs exposed to 0.45 V/cm ( $V_{30}$ ) were 100%. Compared with the existing method, use of the optimization method reduced the volume exposed to 0.90 V/cm ( $V_{60}$ ) by 5% - 23% in three of the nine conditions and reduced the volume exposed to 1.35 V/cm ( $V_{90}$ ) by 26% - 100% under all nine conditions. That is, the higher the electric field strength is the smaller the volume of normal tissue exposed.

Figure 6 shows the 3-D electric field distribution when an electric field is applied to a CT image-based liver cancer patient model using the existing treatment method

Table 2. Comparison of the  $V_{30}$ ,  $V_{60}$ ,  $V_{90}$ ,  $E_{\max}$ , and  $E_{\text{ave}}$  values for each OAR in the (a) lung and (b) liver cancer models.

(a)	Heart			Esophagus			Right Lung		
	BO	AO	Difference	BO	AO	Difference	BO	AO	Difference
$V_{30}$	100	100	0	100	100	0	100	90	10
$V_{60}$	96	85	11	93	71	22	86	61	25
$V_{90}$	89	61	28	74	12	62	68	34	34
$E_{\max}$	4.11	3.58	0.53	2.81	1.53	1.28	4.36	4.00	0.36
$E_{\text{ave}}$	2.22	1.54	0.68	1.63	1.03	0.60	1.76	1.23	0.53
(b)	Stomach			Right Kidney			Left Kidney		
	BO	AO	Difference	BO	AO	Difference	BO	AO	Difference
$V_{30}$	100	100	0	98	97	1	95	95	0
$V_{60}$	58	43	15	91	76	15	85	78	7
$V_{90}$	5	3	2	65	19	46	50	27	23
$E_{\max}$	1.44	1.52	-0.08	2.98	2.85	0.13	2.23	2.13	0.10
$E_{\text{ave}}$	0.99	0.89	0.10	1.55	1.09	0.46	1.29	1.15	0.14

Abbreviations: BO, before application of the optimization algorithm; AO, after application of the optimization algorithm.

and the optimization algorithm to create treatment plans. The differences in the electric-field intensity were not as obvious as in the simple model, although the use of the optimization algorithm increased the volume of the tumor exposed to 3 V/cm slightly, and reduced the volume of the right kidney exposed to 1 - 2 V/cm, with these areas being exposed to electric-field intensity < 1 V/cm. Use of the optimization algorithm also increased the volume of the stomach exposed to < 0.5 V/cm.

Although the overall shapes of the tumor graphs were similar for the existing and the optimization methods (Fig. 7), the maximum electric-field intensities transmitted to the tumor using these two methods were 2.09 V/cm and 2.35 V/cm, respectively, for the lung cancer model (Table 2(a)) and 6.62 V/cm and 6.72 V/cm, respectively, for the liver cancer model (Table 2(b)). The greater maximum electric-field intensity in the liver model compared to the lung cancer model was likely due to the greater electric-field intensity in areas around the electrode. Because liver tumors are closer to the electrode than lung tumors, the maximum electric-field intensity at the former should be higher.

When we compared each of the OARs, we found that the graph lines of the optimization method were generally to the left ( $y$ -axis) of the graph lines of the existing method (Fig. 7). That is, the electric-field intensity transmitted to each OAR was lower by the optimization method than by the existing method. Quantitative analysis also showed that the maximum electric-field intensity was lower for the optimization than for the existing method for all six OARs in both the lung (Table 2(a)) and the liver (Table 2(b)) cancer models, except for the stomach, with differences ranging from 0.10 - 1.28 V/cm. Although the maximum electric-field intensity for the stomach was greater for the optimization than for the existing method, the difference, 0.08 V/cm, was very small. Similarly, comparisons of average electric-field in-



tensities showed that the intensities transmitted to all six OARs was 0.10 - 0.68 V/cm lower with the optimization method.

Assessment of the relative volume of each organ that experienced each level of electric-field intensity showed that the relative volume that experienced more than 0.45 V/cm ( $V_{30}$ ) was the same for four of the six OARs, but in two of them the optimization method affected a smaller volume. The relative volume exposed to 0.90 V/cm ( $V_{60}$ ) was 7% - 25% smaller with the optimization method than the existing method for all six OARs. Moreover, the relative volume exposed to 1.35 V/cm ( $V_{90}$ ) was 2% - 62% smaller with the optimization method for all six OARs. Thus, similar to the simple model, the volume of normal tissue that experienced high levels of electric-field intensity was lower when the optimization method was used.

When an optimization algorithm is used, large and small electrical potentials are generally applied to the electrode near the tumor and the electrode near the OARs, respectively. Therefore, if optimization is used, local electric field intensities applied to the patient's skin below the electrodes can be relatively large or small based on the locations of the electrodes. However, the averages of the electric field intensity applied to the entire skin stayed the same before and after optimization. Our experimental results showed that average electric fields applied to the skin before and after optimization were 0.82 V/cm (0.59 V/cm) per unit skin area and 0.73 V/cm (0.4 V/cm) per unit skin area for the liver (lung), respectively. Although electrode induced local electric fields applied to patient's skin can be relatively large causing skin side effect, this phenomenon can be avoided if the limit of electric field is applied during optimization.

In addition to intensity modulation of the TTFields, one can adjust the electrode size to optimize the electric field inside body. In general, when a small electrode is used, there are several advantages. First, there will be more electrodes (*i.e.*, variables) that can be manipulated to focus the electric field inside body. Second, small electrode can be easily attached to the skin, which is very important issue in TTF therapy. However, if one uses only small electrodes, the high electric field acquired by optimization can be applied to a very small area just below the specific electrode, which might cause a side effect in the skin. On the other hand, when a large electrode is used, it is an advantage to apply a uniform electric field in the body with relatively small electric field on the skin. But, as mentioned before, it might be difficult for large electrode to be attached to the patient's skin completely. Therefore, the appropriate sizes of electrodes are very important in optimization of electric field using intensity modulation and future study is called to investigate the optimal electrode size and field intensity for the best outcome of tumor treating fields.

## IV. CONCLUSION

This study compared the electric-field distributions in the body produced using an optimization algorithm and an existing treatment method. The optimization method resulted in application of a greater electric-field intensity to the tumor while minimizing the electric field intensity at OARs. Use of this method in actual treatment plans may not only increase the effectiveness of the treatment, but also reduce as yet undetermined side effects of TTFields therapy. In the future, we will study the difference in the electric field distribution due to the different electric susceptibilities of organs and prostheses to improve the effect of TTFields therapy.

## ACKNOWLEDGMENTS

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# Influence of Treatment With Tumor-Treating Fields on Health-Related Quality of Life of Patients With Newly Diagnosed Glioblastoma

## A Secondary Analysis of a Randomized Clinical Trial

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**IMPORTANCE** Tumor-treating fields (TTFields) therapy improves both progression-free and overall survival in patients with glioblastoma. There is a need to assess the influence of TTFields on patients' health-related quality of life (HRQoL).

**OBJECTIVE** To examine the association of TTFields therapy with progression-free survival and HRQoL among patients with glioblastoma.

**DESIGN, SETTING, AND PARTICIPANTS** This secondary analysis of EF-14, a phase 3 randomized clinical trial, compares TTFields and temozolomide or temozolomide alone in 695 patients with glioblastoma after completion of radiochemotherapy. Patients with glioblastoma were randomized 2:1 to combined treatment with TTFields and temozolomide or temozolomide alone. The study was conducted from July 2009 until November 2014, and patients were followed up through December 2016.

**INTERVENTIONS** Temozolomide, 150 to 200 mg/m<sup>2</sup>/d, was given for 5 days during each 28-day cycle. TTFields were delivered continuously via 4 transducer arrays placed on the shaved scalp of patients and were connected to a portable medical device.

**MAIN OUTCOMES AND MEASURES** Primary study end point was progression-free survival; HRQoL was a predefined secondary end point, measured with questionnaires at baseline and every 3 months thereafter. Mean changes from baseline scores were evaluated, as well as scores over time. Deterioration-free survival and time to deterioration were assessed for each of 9 preselected scales and items.

**RESULTS** Of the 695 patients in the study, 639 (91.9%) completed the baseline HRQoL questionnaire. Of these patients, 437 (68.4%) were men; mean (SD) age, 54.8 (11.5) years. Health-related quality of life did not differ significantly between treatment arms except for itchy skin. Deterioration-free survival was significantly longer with TTFields for global health (4.8 vs 3.3 months;  $P < .01$ ); physical (5.1 vs 3.7 months;  $P < .01$ ) and emotional functioning (5.3 vs 3.9 months;  $P < .01$ ); pain (5.6 vs 3.6 months;  $P < .01$ ); and leg weakness (5.6 vs 3.9 months;  $P < .01$ ), likely related to improved progression-free survival. Time to deterioration, reflecting the influence of treatment, did not differ significantly except for itchy skin (TTFields worse; 8.2 vs 14.4 months;  $P < .001$ ) and pain (TTFields improved; 13.4 vs 12.1 months;  $P < .01$ ). Role, social, and physical functioning were not affected by TTFields.

**CONCLUSIONS AND RELEVANCE** The addition of TTFields to standard treatment with temozolomide for patients with glioblastoma results in improved survival without a negative influence on HRQoL except for more itchy skin, an expected consequence from the transducer arrays.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT00916409

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← Invited Commentary

+ Supplemental content

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Glioblastoma has a poor prognosis,<sup>1,2</sup> and, as tumors grow, patients often experience a progressive decline in neurologic function and health-related quality of life (HRQoL).<sup>3-7</sup> The current standard of care is not curative but results in prolongation of life. However, extension of survival is meaningful only if patients' functioning and well-being can be retained or improved.<sup>8-11</sup> Therefore, it is important to determine the net clinical benefit of each new treatment or treatment modality introduced; possible benefits of a new treatment, in terms of prolonged survival, have to be carefully weighed against potential negative effects of the treatment on the patients' quality of life.

The current standard of care for patients with newly diagnosed glioblastoma comprises surgical resection to the extent safely feasible followed by radiotherapy with concomitant and maintenance chemotherapy with temozolomide.<sup>12</sup> Tumor-treating fields (TTFields) (Optune; Novocure Ltd) is an antimitotic physical treatment modality<sup>13,14</sup> delivered by a home use medical device with wired transducer arrays placed on the patients' scalp. When added to standard maintenance temozolomide chemotherapy, TTFields has been demonstrated to improve both progression-free survival and overall survival in a randomized clinical trial (NCT00916409).<sup>15</sup>

Treatment with TTFields involves the patient carrying a mobile electrical device for more than 18 hours per day and having 4 arrays of transducers continuously fixed to the shaved scalp. Concerns regarding the influence of wearing the device on patients' HRQoL have therefore been raised.<sup>16,17</sup> The incidence of adverse events was not increased by the addition of TTFields to temozolomide therapy except for an expected mild to moderate skin irritation beneath the electrodes in 52% of patients (severe in 2%). Herein, we report on the influence of treatment with TTFields on the patients' HRQoL, which was a predefined secondary objective of the randomized clinical trial. The present study was conducted from July 2009 until November 2014, and patients were followed up through December 2016.

## Methods

### Study Population

Patients eligible for this study were aged 18 years or older, had newly diagnosed and histologically confirmed supratentorial glioblastoma (World Health Organization grade IV astrocytoma), were progression free after undergoing maximal safe debulking surgery or biopsy, and had completed standard radiotherapy with concomitant temozolomide. Patients were required to have a Karnofsky Performance Status score of at least 70 at the time of enrollment, corresponding to at least being able to perform self-care. Further details on the study population are available elsewhere.<sup>15</sup> All patients provided written informed consent, and the study was approved by the institutional review boards or ethics committees of all participating centers and the relevant competent authorities (eAppendix 1 in Supplement 1); the participants did not receive financial compensation.

### Key Points

**Question** What is the influence of adding tumor-treating fields to the standard treatment on health-related quality of life in patients with glioblastoma?

**Findings** In this secondary analysis of the EF-14 randomized clinical trial, the addition of tumor-treating fields did not negatively influence health-related quality of life except for itchy skin, an expected consequence from the transducer arrays.

**Meaning** Tumor-treating field therapy has previously been shown to prolong both progression-free and overall survival. When considering the net clinical benefit, improved survival without a negative influence on health-related quality of life supports the addition of tumor-treating fields to standard treatment in patients with glioblastoma.

### Study Design and Treatment

This prospective, multicenter, open-label, randomized clinical phase 3 trial recruited 695 patients at 90 medical centers in North America, Europe, the Republic of Korea, and Israel. The trial protocol is available in Supplement 2. The trial was designed to test the efficacy of TTFields in combination with the best standard of care in the treatment of newly diagnosed glioblastoma (ie, radiotherapy with concomitant and adjuvant temozolomide). The primary end point was progression-free survival, with overall survival as a powered secondary end point. Health-related quality of life was a secondary end point. Patients who were progression free after completion of radiochemotherapy were randomized within 4 to 7 weeks at a ratio of 2:1 to receive standard maintenance temozolomide chemotherapy (150-200 mg/m<sup>2</sup> for 5 days every 28 days for 6 cycles) with or without the addition of TTFields. If tolerated well, TTField therapy was to be continued until the second progression or up to 2 years.

Patients in the TTFields plus temozolomide group received continuous TTFields combined with maintenance temozolomide. TTFields were delivered through a portable device in an outpatient setting. Patients receiving TTFields had 4 transducer arrays with 9 insulated electrodes each placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain. Although uninterrupted treatment was recommended, the patient could take short breaks if needed; patients were advised to continue treatment for at least 18 hours a day. More details on the study design and treatment are published elsewhere.<sup>15</sup>

### HRQoL Assessment

The evaluation of HRQoL was performed using the validated European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-C30) and brain module (QLQ-BN20).<sup>18-20</sup> Questionnaires were completed on paper at baseline (prior to randomization) and subsequently every 3 months for up to 12 months. Nine scales and items were preselected as important based on relevance for patients with glioblastoma and hypothesized effects of the TTFields delivery device on patients' HRQoL: global health status; physical, cognitive, role, social, and emotional functioning; itchy skin;



pain; and weakness of legs. We hypothesized that any burden of carrying the device (on physical functioning and itchy skin) or detriment to social and role functioning due to the visibility of the therapy may be balanced by patients' feeling of well-being (global health status and emotional functioning) related to active participation of both the patient and the caregiver in the fight against cancer and increasing patient empowerment. Moreover, we hypothesized that treatment with TTFields would not have an influence on cognitive functioning, pain, and weakness of legs.

### Statistical Analysis

#### Calculation of HRQoL Scores

The items on both questionnaires were scaled and scored using the recommended EORTC procedures.<sup>21</sup> Raw scores were transformed to a linear scale ranging from 0 to 100, with a higher score representing a higher level of functioning or higher level of symptoms. The results of this study are presented in accordance with guidelines for reporting HRQoL in cancer clinical trials and methods.<sup>22-24</sup> Differences of at least 10 points (on a 0-100 scale) were classified as the minimum clinically meaningful change in any HRQoL scale/item.<sup>24</sup>

#### Descriptive Statistics

Descriptive statistics were used to report HRQoL scores as well as the sociodemographic and clinical variables for the population of patients who completed at least 1 HRQoL scale at baseline separately for both treatment groups. Means and SDs or medians and ranges were calculated for continuous variables depending on the distribution of the variable. Frequencies and percentages were calculated for nominal variables. Differences between arms were tested using a 2-sided  $\chi^2$  test or an independent 2-tailed, unpaired *t* test or Mann-Whitney test at an  $\alpha$  value of .05 for each variable.

Adherence to HRQoL assessments was calculated as the number of forms received divided by the number of forms expected at every assessment. Patients who completed the assessments at the time of progression were included in this analysis.

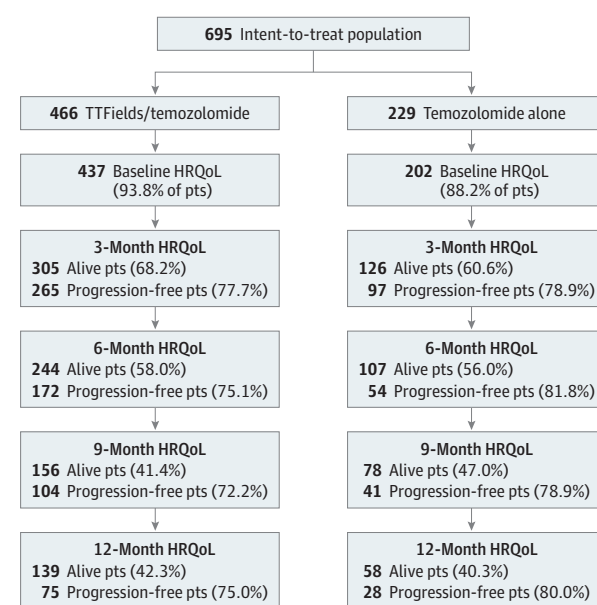
#### HRQoL Scores Over Time

Mean HRQoL scores over time were calculated as well as the mean changes from baseline. A stable HRQoL score was defined as a change of less than 10 points, and a change of 10 or more points indicated a deterioration or improvement depending on the scale or item. Mean change from baseline was plotted to evaluate the longitudinal course of patients' experience of disease and treatment, and a linear mixed-model repeated-measures analysis was used to estimate the treatment effect over time. A sensitivity analysis of complete cases using multiple imputations with a predictive mean matching regression model was used to check the robustness of the treatment effect over time. An additional sensitivity analysis used a repeated-measures model that assumes there is random variation among participants that is related to the time of dropout.

#### Stable or Improved HRQoL During the Progression-Free Period

The percentage of patients with stable (<10-point change) or improved ( $\geq$ 10-point change) HRQoL during the progression-

Figure 1. Consort Diagram



Data are the number and percentage of patients in the categories (baseline, alive, and progression-free) who completed the health-related quality-of-life (HRQoL) questionnaire at the indicated times. pts indicates patients; TTFields, tumor-treating fields.

free period, thus excluding the HRQoL assessment at progression, was determined separately for both treatment arms. This calculation was based on the total number of patients with a valid baseline HRQoL assessment and at least 1 additional follow-up assessment. Moreover, the area under the curve of stable or improved HRQoL for the entire duration of stability or improvement was determined, and differences between arms were assessed with the trapezoidal method (eAppendix 2 in Supplement 1).

#### Deterioration-Free Survival and Time to Deterioration

Deterioration-free survival was defined as the time to a greater than 10-point deterioration in scores from baseline without a subsequent 10-point or more improvement in scores compared with baseline, progressive disease, or death in the absence of a previous definitive deterioration before the next assessment. Disease progression was included as a surrogate measure. Data were censored at the last HRQoL assessment date for patients with a change of less than 10 points, patients who did not progress, or patients who died after 9 weeks since the last assessment. Data for patients with missing baseline scores were not included, and patients missing all postbaseline HRQoL assessments were censored at randomization. Time to deterioration (TTD) was defined similarly to deterioration-free survival, with the exception that progressive disease was excluded as an event (ie, nonmissing HRQoL data beyond progression were included). Kaplan-Meier methodology was used to estimate deterioration-free survival and TTD distributions and median times, and 95% CIs were computed using the Greenwood formula. The difference between treatment arms



Table 1. Baseline Demographic and Disease Characteristics

Characteristic	TTFields Plus Temozolomide (n = 437)	Temozolomide (n = 202)	All Patients (N = 639)	P Value
Age, y				
Mean (SD)	54.6 (11.4)	55.2 (11.6)	54.8 (11.5)	.50
Median (range)	56.0 (19-83)	57.0 (19-80)	56.0 (19-83)	
Sex, No. (%)				
Male	297 (68.0)	140 (69.3)	437 (68.4)	.73
Female	140 (32.0)	62 (30.7)	202 (31.6)	
Antiepileptic medication at baseline, No. (%)	174 (39.8)	79 (39.1)	253 (39.6)	.87
Corticosteroid therapy at baseline, No. (%)	129 (29.5)	60 (29.7)	189 (29.6)	.96
Region, No. (%)				
United States	203 (46.5)	97 (48.0)	300 (46.9)	.71
Canada, Europe, Israel, and Korea	234 (53.5)	105 (52.0)	339 (53.1)	
Extent of resection, No. (%)				
Biopsy	55 (12.6)	24 (11.9)	79 (12.4)	.97
Partial resection	149 (34.1)	70 (34.7)	219 (34.3)	
Gross total resection	233 (53.3)	108 (53.5)	341 (53.4)	
Tumor position, No. (%) <sup>a</sup>				
Corpus callosum	23 (5.3)	12 (5.9)	35 (5.5)	.66
Frontal lobe	177 (40.5)	74 (36.6)	251 (39.3)	
Occipital lobe	55 (12.6)	24 (11.9)	79 (12.4)	
Parietal lobe	138 (31.6)	78 (38.6)	216 (33.8)	
Temporal lobe	179 (41.0)	81 (40.1)	260 (40.7)	
Missing	2 (<1)	2 (1.0)	4 (0.6)	
Tumor location, No. (%) <sup>a</sup>				
Left	202 (46.2)	84 (41.6)	286 (44.8)	.65
Right	234 (53.5)	116 (57.4)	350 (54.8)	
Both	4 (0.9)	2 (1.0)	6 (0.9)	
Corpus callosum	14 (3.2)	9 (4.5)	23 (3.6)	
Completed radiotherapy, No. (%)				
<57 Gy	20 (4.6)	10 (5.0)	30 (4.7)	.38
60 Gy (standard; ±5%)	399 (91.3)	188 (93.1)	587 (91.9)	
>63 Gy	15 (3.4)	3 (1.5)	18 (2.8)	
Missing	3 (0.7)	1 (0.5)	4 (0.6)	
Karnofsky performance score				
Median (range)	90 (60-100)	90 (70-100)	90 (60-100)	.26
Baseline Mini-Mental State Examination score available, No. (%)	429 (98.2)	194 (96.0)	623 (97.5)	
≤26	81 (18.9)	43 (22.2)	124 (19.9)	.34
27-30	348 (81.1)	151 (77.8)	499 (80.1)	
Cycles (months) of treatment with TTFields		NA	NA	NA
No.	425			
Mean (SD)	12.5 (11.8)			
Median (range)	8.3 (0-82)			
Cycles of treatment with temozolomide				
No.	430	192	622	.02
Mean (SD)	8.9 (8.3)	7.5 (6.2)	8.5 (7.8)	
Median (range)	6.2 (0-51)	5.5 (0-33)	5.9 (0-51)	
Adherence to TTFields therapy <sup>b</sup>	327 (74.8)	NA	NA	NA

Abbreviations: Gy, gray; NA, not applicable; TTFields, tumor-treating fields.

<sup>a</sup> Multiple locations possible.

<sup>b</sup> Defined as use of the device 75% or more of the time during the first 3 months of treatment.

was compared using a 2-sided stratified log-rank test. Hazard ratios were estimated using a stratified (for extent of resection and *MGMT* status) Cox proportional hazards regression model.

SAS, version 9.4 (SAS Institute) was used for all statistical analyses, and comparisons between groups were based on the intent-to-treat principle. *P* values <.05 were considered to be



Figure 2. Changes in Global Health Status and Itchy Skin



Mean changes in points on health-related quality of life scales from baseline in global health status (A) and itchy skin with (B) with tumor-treating fields (TTFields) plus temozolomide compared with temozolomide alone. No change,

between 0 and 10 points; improvement and deterioration, changes of 10 points or more. Error bars indicate SD.

statistically significant. The Hochberg procedure was used to adjust for the multiplicity of treatment comparisons in the pre-selected HRQoL scales analyses.

## Results

### Patients

A total of 695 patients were randomly assigned in a 2:1 ratio to TTFields plus temozolomide ( $n = 466$ ) or temozolomide alone ( $n = 229$ ). A total of 639 (91.9%) patients completed at least 1 HRQoL scale at baseline: 437 (93.8%) of those in the TTFields plus temozolomide arm and 202 (88.2%) patients in temozolomide-alone arm (Figure 1). The baseline demographics of the patients who provided HRQoL data were comparable to those of the intention-to-treat population<sup>15</sup> and were well balanced between treatment arms in this subpopulation (Table 1).

### HRQoL Completion Rates and Baseline Scores

Adherence to HRQoL assessments decreased from 91.9% at baseline to 65.8% (431 of 655 patients alive) at 3 months and dropped to 41.7% (197 of 473 patients alive) at 12 months of follow-up (Figure 1). Mean and median baseline HRQoL scores were comparable between arms for all preselected scales/items (eTable 1 in Supplement 1), as well as the exploratory scales and items. Reference values of HRQoL scores of a healthy general population<sup>25</sup> were available for 7 of 9 predefined scales and items (except itchy skin and weakness of legs). Patients with glioblastoma after completion of radiochemotherapy showed clinically relevant worse functioning or more symptoms compared with the general population on all scales except pain, which was similar.<sup>25</sup>

### Mean Changes in HRQoL From Baseline and the Repeated-Measures Mixed-Effect Model

Mean changes in HRQoL over time for the global health status is presented in Figure 2A and for all 9 predefined HRQoL scales

in the eFigure in Supplement 1. Throughout the 12-month assessment period, mean changes from baseline were stable (<10-point change from baseline) for all 9 predefined HRQoL scales in both treatment arms (eFigure in Supplement 1) with the exception of itchy skin (Figure 2B). For itchy skin, a clinically relevant deterioration (ie, an increase in itchy skin) compared with baseline was seen at the month 3 evaluation in the TTFields plus temozolomide arm (mean [SD] increase, 10.4 [30.1] points vs an improvement of 2.3 [24.4] points in the temozolomide arm). For differences between treatment arms, patients treated with TTFields plus temozolomide had significantly and clinically relevant worse itchy skin at 3, 6, and 9 months than patients treated with temozolomide alone, but not at 12 months (mean [SD] increase of 10.4 [30.1] in the TTFields plus temozolomide arm vs a decrease of 2.3 [24.4] in the temozolomide-alone arm,  $P = .005$ ; increase of 8.1 [31.6] in the TTFields plus temozolomide arm vs a decrease of 4.2 [31.4] in the temozolomide-alone arm,  $P = .008$ ; increase of 5.3 [28.0] in the TTFields plus temozolomide arm vs a decrease of 5.2 [29.6] in the temozolomide-alone arm,  $P = .04$ ; increase of 4.6 [32.8] in the TTFields plus temozolomide arm vs a decrease of 1.9 [36.9] in the temozolomide-alone arm,  $P = .66$ , respectively). For all other scales, there were no statistically significant or clinically relevant differences between treatment arms.

The repeated-measures mixed-effect model supported this finding, with no statistically significant difference between treatment arms in HRQoL scores over time in any predefined scale or item except for itchy skin ( $P < .001$ ), which was worse in the TTFields plus temozolomide arm (eTable 2 in Supplement 1). The sensitivity analyses showed that the results of the linear mixed model were robust.

### Stable or Improved HRQoL During Progression-Free Time

Compared with baseline, more patients in the TTFields plus temozolomide arm compared with the temozolomide-alone arm reported stable or improved scores for global health status (53.5% vs 38.0%, respectively,  $P = .001$ ), physical func-



Table 2. Stable or Improved Health-Related Quality of Life During Progression-Free Time

Characteristic	TTFields Plus Temozolomide (n = 361)	Temozolomide (n = 142)	P Value	α Value
<b>Pain</b>				
Stable/improved from baseline, No./No. (%)	205/361 (56.8)	51/142 (35.9)	<.001	.05
Median duration (95% CI), mo	6.2 (5.9 to 7.0)	6.3 (5.6 to 9.1)	.88	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 0)	0 (0 to 0)	.80	
<b>Global health status</b>				
Stable/improved from baseline, No./No. (%)	192/359 (53.5)	53/141 (37.6)	.001	.025
Median duration (95% CI), mo	6.3 (5.9 to 7.4)	7.9 (5.9 to 9.8)	.24	
Median CFB AUC until last stable/improved status (95% CI)	24.4 (11.9 to 35.0)	65.9 (13.1 to 121.3)	.13	
<b>Physical functioning</b>				
Stable/improved from baseline, No./No. (%)	195/361 (54.0)	54/142 (38.0)	.001	.017
Median duration (95% CI), mo	6.2 (5.9 to 8.2)	9.1 (5.9 to 9.8)	.21	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 18.7)	0 (0 to 30.0)	.53	
<b>Weakness of legs</b>				
Stable/improved from baseline, No./No. (%)	206/351 (58.7)	58/138 (42.0)	.001	.013
Median duration (95% CI), mo	6.3 (6.0 to 8.3)	9.1 (5.9 to 9.8)	.08	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 0)	0 (0 to 0)	.51	
<b>Cognitive functioning</b>				
Stable/improved from baseline, No./No. (%)	181/359 (50.4)	55/142 (38.7)	.02	.01
Median duration (95% CI), mo	6.0 (4.9 to 6.5)	6.2 (5.7 to 9.6)	.65	
Median CFB AUC until last stable/improved status (95% CI)	26.3 (0 to 48.6)	0 (0 to 93.3)	.37	
<b>Emotional functioning</b>				
Stable/improved from baseline, No./No. (%)	196/359 (54.6)	62/142 (43.7)	.03	.008
Median duration (95% CI), mo	6.3 (6.0 to 8.3)	7.7 (5.8 to 9.4)	.38	
Median CFB AUC until last stable/improved status (95% CI)	22.6 (5.8 to 35.0)	25.2 (0 to 54.4)	.73	
<b>Social functioning</b>				
Stable/improved from baseline, No./No. (%)	173/359 (48.2)	58/142 (40.8)	.14	.007
Median duration (95% CI), mo	6.2 (5.9 to 7.1)	6.7 (5.9 to 9.6)	.40	
Median CFB AUC until last stable/improved status (95% CI)	16.5 (0 to 47.2)	0 (0 to 54.4)	.90	
<b>Role functioning</b>				
Stable/improved from baseline, No./No. (%)	173/361 (47.9)	58/141 (41.1)	.17	.006
Median duration (95% CI), mo	5.9 (4.4 to 6.3)	7.3 (5.7 to 9.3)	.27	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 25.0)	46.7 (0 to 75.8)	.34	
<b>Itchy skin</b>				
Stable/improved from baseline, No./No. (%)	148/349 (42.4)	64/137 (46.7)	.39	.0056
Median duration (95% CI), mo	6.0 (4.7 to 6.3)	6.7 (5.6 to 9.4)	.37	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 0)	0 (−102.2 to 0)	.19	

Abbreviations: AUC, area under the curve; CFB, change from baseline; TTFields, tumor-treating fields.

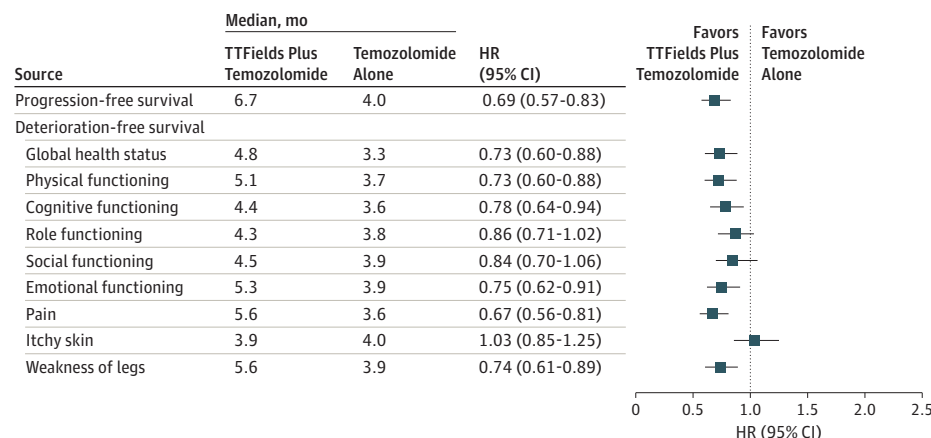
tioning (54.0% vs 37.0%, respectively;  $P = .001$ ), pain (56.8% vs 35.9%, respectively;  $P < .001$ ), and weakness of legs (58.7% vs 42.0%, respectively;  $P = .001$ ) but not in any of the other HRQoL scales and items. However, the duration of stable or improved HRQoL was shorter in the TTFields plus temozolomide arm, although not significantly different from the temo-

zolomide arm for any of the HRQoL scales and items. Overall, with a combination of these measures, the area under the curve analysis showed no significant differences between treatment arms for any of the HRQoL scales and items, indicating a similar HRQoL between treatment arms while patients did not experience tumor progression (Table 2).

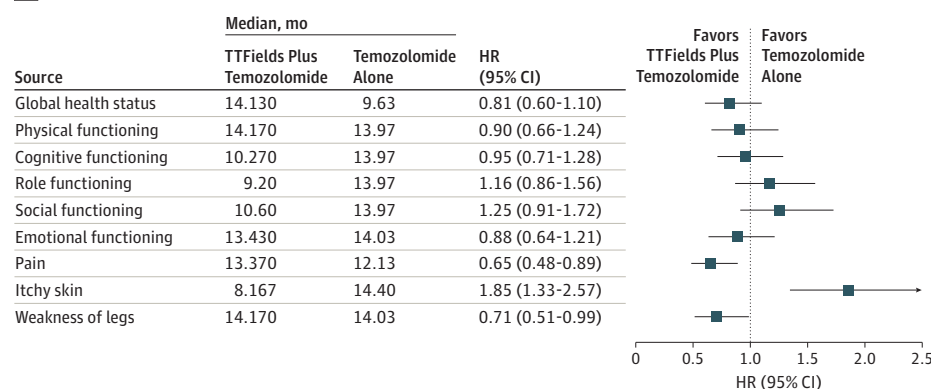


Figure 3. Deterioration-Free Survival and Time to Deterioration

## A Deterioration-free survival



## B Time to deterioration



Deterioration-free survival (A) and time to deterioration (B) for health-related quality-of-life domains in patients who received tumor-treating fields (TTFields) plus temozolomide compared with temozolomide alone. HR indicates hazard ratio.

## Deterioration-Free Survival and TTD

The addition of TTFields to standard temozolomide chemotherapy resulted in statistically significant longer deterioration-free survival in global health status, physical and emotional functioning, pain, and weakness of legs (Figure 3A and eTable 2 in Supplement 1); the significant difference remained after correction for multiple testing. When progression was removed as a deterioration event (TTD), there was no negative influence of TTFields plus temozolomide treatment on the TTD of HRQoL (Figure 3B) except for itchy skin, which was worse in the TTFields plus temozolomide arm (8.2 vs 14.4 months). In contrast, the addition of TTFields to temozolomide resulted in a statistically significant prolongation until deterioration for pain (13.4 vs 12.1 months,  $P < .01$ ). There were no other significant differences in TTD between arms (Figure 3B).

## Discussion

In our detailed analysis of HRQoL during therapy with TTFields in addition to temozolomide, no significant difference was found between the groups in patients' HRQoL over time except for the skin reaction. As expected, itchy skin was reported more frequently in patients treated with TTFields be-

cause of the transducer arrays that have to be placed on the scalp of the patient. Consistently, over half of the patients also reported skin irritation as an adverse event. We had hypothesized that patients treated with TTFields may have better HRQoL in some domains as a result of active participation in the fight against cancer and the frequent interactions between patients and caregivers and device technicians regarding the device. However, on a group level, global health status and emotional functioning were not significantly different between treatment arms. Likewise, our hypotheses that the addition of TTFields would result in worse role and social functioning (due to the visibility of the device) and worse physical functioning were not confirmed. In line with our hypotheses, cognitive functioning, pain, and weakness of legs were not negatively affected by the addition of TTFields to temozolomide treatment. Most relevant for patients, HRQoL was maintained (in 8 of 9 of the predefined scales/items) over time. Combining the results of the survival and HRQoL analyses suggests that the addition of TTFields to adjuvant temozolomide is of value to patients with glioblastoma.

Patients who received TTFields had significantly longer deterioration-free survival compared with those in the temozolomide-alone arm for global health status (4.8 vs 3.3 months;  $P < .01$ ), physical (5.1 vs 3.7 months;  $P < .01$ ) and



emotional functioning (5.3 vs 3.9 months;  $P < .01$ ), pain (5.6 vs 3.6 months;  $P < .01$ ), and weakness of legs (5.6 vs 3.9 months;  $P < .01$ ). For the other scales and items, there was no significant difference in deterioration-free survival between the 2 treatment arms. The prolonged deterioration-free survival for these scales is explained by the extended progression-free survival for patients in the combined TTFields plus temozolomide arm, as progressive disease is included as an event in this analysis. Therefore, TTD analyses, excluding progressive disease as an event, is important to illustrate the influence of a treatment on HRQoL: TTD was not significantly different across any HRQoL scale or item in TTFields-treated patients except for pain and itchy skin, indicating that treatment with TTFields had an influence only on the level of pain and itchy skin. In patients treated with TTFields, TTD was significantly longer for pain (13.4 vs 12.1 months;  $P < .01$ ) and significantly shorter for itchy skin (8.2 vs 14.4 months;  $P < .001$ ). The difference between deterioration-free survival and TTD indicates the importance of disease progression (rather than treatment) as a key event driving HRQoL decline, as suggested by previous studies.<sup>26,27</sup> Moreover, in only 1% of patients, regardless of treatment arm, was a clinically relevant improvement in HRQoL seen after initial deterioration, supporting this observation. Taken together, the results of the deterioration-free survival and TTD analyses support the results of the longitudinal analysis by showing that the addition of TTFields to the standard of care did not adversely affect HRQoL. In fact, the delay in TTD for pain seen in TTFields-treated patients may reflect a delay in the occurrence of tumor-related headaches (although not significant, patients in the TTFields plus temozolomide arm had a longer TTD compared with patients in the temozolomide-alone arm for headaches: hazard ratio, 0.77; 95% CI, 0.54-1.10;  $P = .16$ ). Future studies are needed to better understand this finding, as the median TTD values for pain were longer than the median progression-free survival for both arms.

## Limitations

A common problem in many cancer clinical trials, as in this study, is missing HRQoL data. This absence is especially apparent during the follow-up period, hampering longitudinal data analysis. Patients with better prognostic factors and a good treatment response will be overrepresented at later stages.<sup>28,29</sup> However, our mixed-model analyses, accounting for missing data, confirmed the results found in the mean change from baseline analyses. Another limitation of clinical trials is generalizability of results—patients in clinical trials may not be representative of a general glioblastoma population. Patients in this trial were included only if they successfully completed the combined radiochemotherapy. In addition, it may be that not all patients are prepared to accept wearing the TTFields device. Nevertheless, patients participating in this trial were similar with respect to clinical characteristics to those participating in the EORTC 26981 study<sup>12</sup> comparing radiotherapy alone with radiotherapy plus temozolomide. Lastly, many factors may affect HRQoL, such as age, comorbidity, tumor characteristics, previous antitumor treatment (eg, radiation dose), and supportive treatment. However, it is unlikely that these factors influenced our conclusion, as the objective of this study was to compare HRQoL results between 2 treatment arms in which patients were similar due to randomization.

## Conclusions

Use of TTFields prolongs progression-free and overall survival in patients with glioblastoma. The addition of this novel device-delivered treatment neither negatively affects nor improves functioning and well-being of the patient, including critical HRQoL issues, such as role, social, and physical functioning. Patients reported more itchy skin, which is a direct and expected consequence of the placement of transducer arrays on the patients' scalp. Considering the net clinical benefit, our HRQoL data support the addition of TTFields to standard therapy in patients with glioblastoma.

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# Increased compliance with tumor treating fields therapy is prognostic for improved survival in the treatment of glioblastoma: a subgroup analysis of the EF-14 phase III trial

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## Abstract

**Background** Tumor treating fields (TTFields) is a non-invasive, antimitotic therapy. In the EF-14 phase 3 trial in newly diagnosed glioblastoma, TTFields plus temozolomide (TTFields/TMZ) improved progression free (PFS) and overall survival (OS) versus TMZ alone. Previous data indicate a  $\geq 75\%$  daily compliance improves outcomes. We analyzed compliance data from TTFields/TMZ patients in the EF-14 study to correlate TTFields compliance with PFS and OS and identify potential lower boundary for compliance with improved clinical outcomes.

**Methods** Compliance was assessed by usage data from the NovoTTF-100A device and calculated as percentage per month of TTFields delivery. TTFields/TMZ patients were segregated into subgroups by percent monthly compliance. A Cox proportional hazard model controlled for sex, extent of resection, *MGMT* methylation status, age, region, and performance status was used to investigate the effect of compliance on PFS and OS.

**Results** A threshold value of 50% compliance with TTFields/TMZ improved PFS (HR 0.70, 95% CI 0.47–1.05) and OS (HR 0.67, 95% CI 0.45–0.99) versus TMZ alone with improved outcome as compliance increased. At compliance  $> 90\%$ , median survival was 24.9 months (28.7 months from diagnosis) and 5-year survival rate was 29.3%. Compliance was independent of gender, extent of resection, *MGMT* methylation status, age, region and performance status (HR 0.78;  $p=0.031$ ; OS at compliance  $\geq 75\%$  vs.  $< 75\%$ ).

**Conclusion** A compliance threshold of 50% with TTFields/TMZ correlated with significantly improved OS and PFS versus TMZ alone. Patients with compliance  $> 90\%$  showed extended median and 5-year survival rates. Increased compliance with TTFields therapy is independently prognostic for improved survival in glioblastoma.

**Keywords** Glioblastoma · Tumor treating fields · Compliance · Monthly usage

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## Introduction

Glioblastoma (GBM) is the most common and aggressive adult brain tumor, accounting for 56% of all gliomas and 15% of all primary brain tumors with an annual incidence in the United States that increases with age—ranging from 0.2 per 100,000 in 0–19 year old population to the highest rate of 15.3 per 100,000 in the 75–84 year old population [1]. Glioblastoma remains incurable with a median survival of only 15 months until recently [2]. The previous standard treatments for newly diagnosed GBM include maximally safe surgical resection followed by radiation therapy (RT) and adjuvant temozolomide (TMZ) chemotherapy [3].

Tumor treating fields (TTFields) are a unique treatment modality [4, 5] for GBM that affects rapidly dividing glioma cells through the action of low-intensity, intermediate



frequency (200 kHz) alternating electric fields [6–9] that act on microtubules and septin fibers of proliferating cancer cells to disrupt mitosis, inducing mitotic cell death, mitotic catastrophe, and cellular stress characterized by autophagy, and endoplasmic reticulum stress [6–13]. TTFields inhibit DNA damage repair by the expression of DNA repair genes in the BRCA1 pathway [14] and impair cellular migration and invasion [15]. TTFields increases cell death when combined with anti-PD1, chemotherapy and radiotherapy [16–19].

The phase 3 EF-11 study of TTFields in recurrent GBM demonstrated comparable efficacy to best physician choice chemotherapy without treatment limiting systemic adverse effects [20]. Post hoc analysis of the EF-11 trial data showed significantly longer median OS with TTFields at compliance rate of  $\geq 75\%$  ( $\geq 18$  h daily) versus those with a  $< 75\%$  compliance rates [21] and high compliance rates of  $> 90\%$  with EF-11 responders [22]. The Patient Registry Dataset (PRiDe) showed significant improvement in median OS at daily compliance rates of  $\geq 75\%$  versus  $< 75\%$  [23]. The phase 3 EF-14 study in newly diagnosed GBM demonstrated that TTFields plus maintenance TMZ therapy significantly improved PFS and OS without decline in health related quality of life (HRQOL) versus TMZ alone [24–26]. The National Comprehensive Cancer Network (NCCN) has recently (2018) recommended TTFields with TMZ as a standard Category 1 treatment option for newly diagnosed GBM [27].

Unlike systemic therapies, TTFields are only active against cancer cells while the transducer arrays are placed on the scalp and the field generator is continuously administering alternating electric fields of a specific intensity (200 KHz) for GBM. There are no peak-trough fluctuations or half-life associated with TTFields. The specificity of TTFields on anti-mitotic activity of rapidly dividing glioma cells, while sparing normal cell division, enables near continuous cancer therapy with minimal systemic adverse effects. Therefore, active compliance with TTFields therapy is a critical parameter for clinical benefit.

The objective of this subgroup analysis of the EF-14 phase III trial data was to analyze compliance data to correlate TTFields compliance with PFS and OS and identify potential lower boundary for compliance rates with improved clinical outcomes.

## Methods

This subgroup analysis is based on TTFields plus TMZ and TMZ alone patient data from the EF-14 study [24]. The EF-14 trial was a randomized, open-label trial, which enrolled 695 newly diagnosed patients with GBM whose tumor was either resected or biopsied and had also

completed concomitant radiation therapy with adjuvant TMZ therapy. Patients were randomized 2:1 to TTFields plus maintenance TMZ chemotherapy ( $n = 466$ ) or temozolomide alone ( $n = 229$ ). Temozolomide was administered to both groups ( $150\text{--}200\text{ mg/m}^2$ ) for 5 days per 28-day cycle (6–12 cycles). The median time from diagnosis to randomization in both groups was 3.8 months [24].

The primary outcome of this subgroup analysis was to assess the percentage of monthly TTFields compliance as an independent predictor of PFS and OS compared with patients in the TMZ alone treatment group. Compliance data are derived from the internal computerized log file of each NovoTTF-100A (Optune®) device. Percent of the total treatment time during which the NovoTTF-100A treated patients actually received treatment was calculated by analyzing the log file of each device and dividing the total device ‘ON’ time by the prescribed number of 1 month treatment courses.

Patient compliance was calculated as the average percentage of each month the system was delivering TTFields. Progression-free survival and OS data from the TTFields plus TMZ treated group were analyzed in subgroups based on monthly compliance levels of  $< 75\%$  or  $\geq 75\%$  and finer monthly compliance bins of 0 to  $\leq 30\%$ , 30% to  $\leq 50\%$ , 50% to  $\leq 60\%$ , 60% to  $\leq 70\%$ , 70% to  $\leq 80\%$ , 80% to  $\leq 90\%$ , 90% to  $\leq 100\%$ .

The PFS and OS survival curves were constructed using the Kaplan–Meier method. Cox proportional hazards model was used to analyze treatment compliance as an independent predictor of survival controlling for treatment group, sex, *MGMT* methylation status, resection status, Karnofsky Performance Status (KPS) and country of residence (United States versus outside the United States). The threshold for significant interactions in the model was specified at an  $\alpha$  of 0.05.

## Results

In the EF-14 study, 466 patients were randomized to the TTFields plus TMZ therapy group and 229 were randomized to the TMZ alone group [24]. The patient disposition is shown in Supplementary Fig. 1. In summary, for the TTFields plus TMZ group—the majority of patients were men (68%) with a median age of 56 years, and a KPS of 90% [24]. The *MGMT* promoter region was unmethylated in 54% and methylated in 36% patients in the TTFields plus TMZ group [24]. Table 1 shows the baseline demographic characteristics of the TTFields plus TMZ group separated into subgroups based on percent compliance. Overall, the separate percent compliance groups were matched in baseline characteristics both with each other and the full data set of the primary study.



**Table 1** Baseline demographics by TTFields percent average daily compliance

% Compliance	0 to ≤30 (n=22)	30 to ≤50 (n=40)	50 to ≤60 (n=42)	60 to ≤70 (n=46)	70 to ≤80 (n=91)	80 to ≤90 (n=166)	90 to ≤100 (n=43)	TMZ alone (n=229)
Median age, years (range)	55.5 (30–70)	57.5 (25–78)	54.5 (22–79)	55.0 (20–83)	56.0 (30–78)	56.0 (28–80)	52.0 (19–68)	57.0 (19–80)
KPS, median (range)	80.0 (70–100)	90.0 (70–100)	90.0 (70–100)	90.0 (60–100)	90.0 (70–100)	90.0 (70–100)	90.0 (70–100)	90.0 (70–100)
Extent of resection, n (%)								
Biopsy only	6 (27)	4 (10)	2 (5)	8 (17)	10 (11)	23 (14)	5 (12)	29 (13)
Partial/com- plete	5 (23)	14 (35)	18 (43)	15 (33)	34 (37)	52 (31)	11 (26)	77 (34)
Gross total resection	11 (50)	22 (55)	22 (52)	23 (50)	47 (52)	91 (55)	27 (63)	123 (54)
MGMT tissue available and tested, n (%)	16 (73)	34 (85)	39 (93)	35 (76)	71 (78)	142 (86)	37 (86)	185 (81)
Methylated	5 (31.3)	14 (41.2)	12 (30.8)	13 (37.1)	24 (33.8)	49 (34.5)	15 (40.5)	77 (41.6)
Unmethyl- ated	10 (62.5)	15 (44.1)	24 (61.5)	20 (57.1)	41 (57.7)	76 (53.5)	17 (45.9)	95 (51.4)
Invalid	1 (6.3)	5 (14.7)	3 (7.7)	2 (5.7)	6 (8.5)	17 (12.0)	5 (13.5)	13 (7.0)

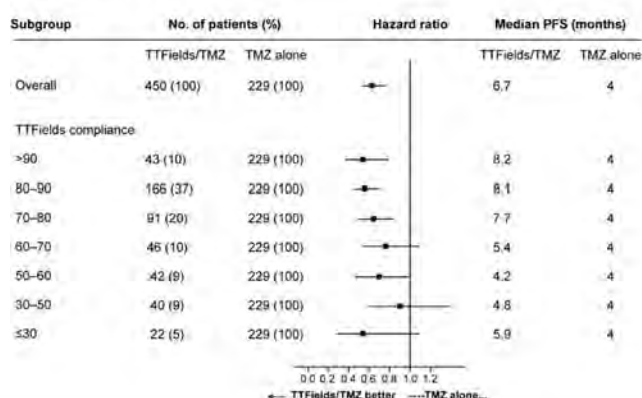
Analysis of the more refined rates of compliance (smaller bin sizes) shows a trend in favor of longer PFS and OS with progressively higher levels of monthly compliance. A threshold value of  $\geq 50\%$  average monthly compliance with TTFields plus TMZ (Fig. 1) was needed to show an extension of PFS (HR 0.70, 95% CI 0.47–1.05) and OS (HR 0.67, 95% CI 0.45–0.99) compared to TMZ alone. Both PFS and OS were extended when compliance was increased beyond 50%, indicating progressively increased gains in PFS and OS as compliance increases.

Patients with TTFields plus TMZ compliance levels of  $> 90\%$  showed maximum survival benefits (Fig. 2), with a

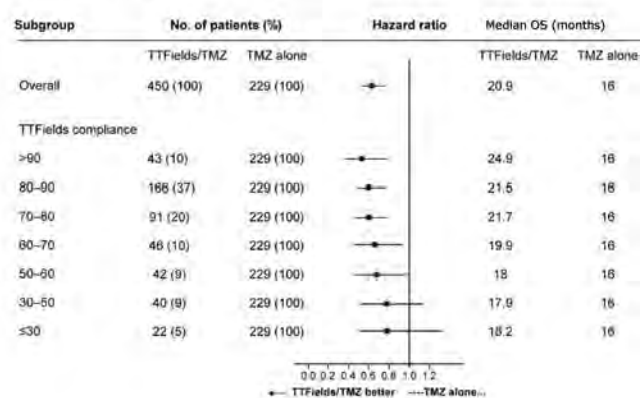
median PFS of 8.2 months for the TTFields plus TMZ group compared to 4.0 months in the TMZ alone group (HR 0.538, 95% CI 0.365–0.794;  $p=0.0047$ ) and an OS of 24.9 months (28.7 months from diagnosis since time from diagnosis to randomization was 3.8) in the TTFields plus TMZ arm compared to 16.0 months in the TMZ alone group respectively (HR 0.522, 95% CI 0.347–0.787;  $p=0.0007$ ). TTFields plus TMZ treated patients with  $> 90\%$  compliance rate had a 5-year survival rate of 29.3% (Fig. 3).

A compliance level of  $\geq 75\%$  monthly duration of treatment with TTFields plus TMZ was an independent predictor of OS, as was methylated *MGMT* status, age and KPS

### Progression-Free Survival



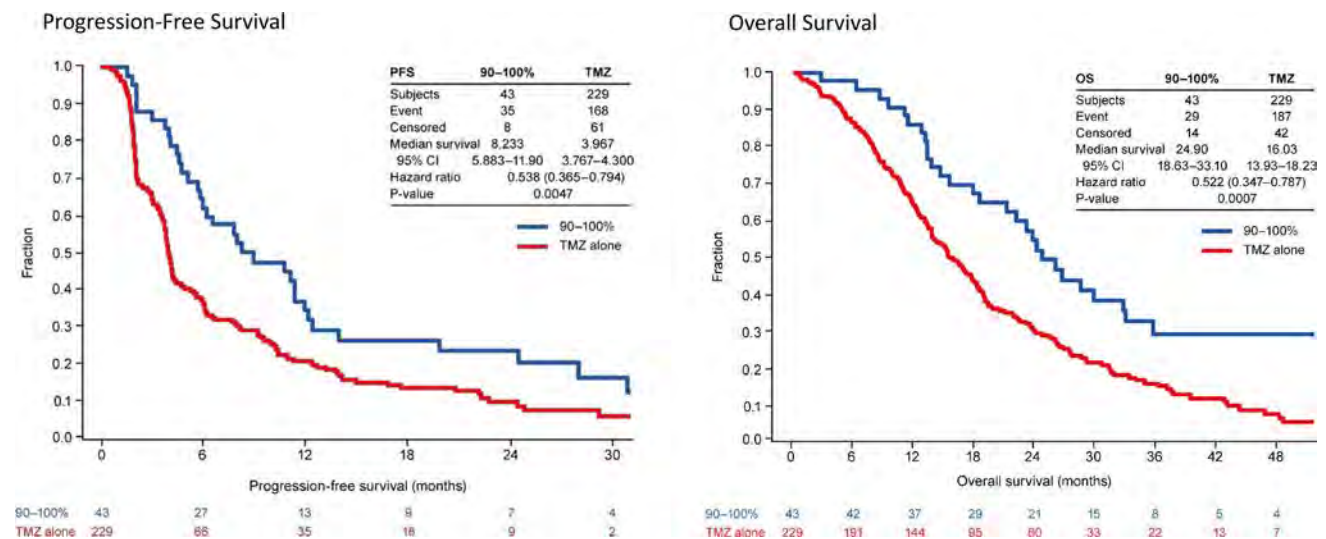
### Overall Survival



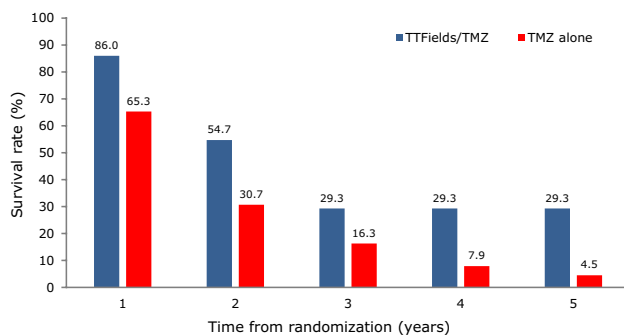
**Fig. 1** Forest plots show the effect of treatment compliance with TTFields plus TMZ on PFS and OS. A threshold value of 50% compliance with TTFields plus TMZ was needed to show a significant extension of OS compared to TMZ alone. Both PFS and OS were

extended with treatment compliance levels  $> 50\%$ . A trend in favor of longer PFS and OS was seen with higher rates of treatment compliance





**Fig. 2** Newly diagnosed GBM patients had maximal treatment benefit from TTFields plus TMZ with compliance rates >90% with a median overall survival of 24.9 months (28.7 months from diagnosis)



**Fig. 3** The annual survival rate was highest for newly diagnosed GBM patients with compliance rates >90% with a 29.3% survival rate over 5 years from randomization

(Table 2) regardless of treatment arm (reference values—compliance <75%), sex (male), resection (biopsy), *MGMT* (negative), and region (USA).

## Discussion

In this subgroup analysis of EF-14 study patients receiving TTFields plus TMZ treatment, a threshold value of  $\geq 50\%$  average compliance with TTFields plus TMZ showed an extension of PFS and OS compared to TMZ alone. Further, patients with monthly compliance >90% had maximal survival benefit with a median survival of 24.9 months (28.7 months from diagnosis) and a 5-year survival of 29.3%. This effect was independent of other prognostic factors such as performance status, age, and *MGMT* methylation status.

**Table 2** Cox proportional hazards model for OS in TTFields/TMZ patients

Parameter	Parameter value	Hazard ratio	Two-sided p-value
Treatment arm	Compliance $\geq 75\%$	0.781	0.031
Sex	Female	0.800	0.069
Resection status	Gross total resection	0.789	0.202
	Partial resection	0.777	0.181
MGMT status	Methylated	0.510	<0.001
	Unknown	0.810	0.131
Region	Outside the USA	1.157	0.199
Age		1.021	<0.001
KPS		0.984	0.006

Compliance was an independent predictor of OS in the full 5-year dataset ( $\geq 75\%$  vs. <75%) [24].

Post hoc analysis of the EF-11 trial data demonstrated longer median OS in TTFields treated recurrent GBM patients with a compliance rate of  $\geq 75\%$  compared to those with a <75% compliance rate (7.7 vs. 4.5 months;  $p=0.042$ ) [21]. This early analysis supported a preliminary target level for treatment compliance ( $\geq 75\%$ ) in clinical practice as well as evidence for a trend suggesting that higher levels of survival benefit were associated with increasing compliance [21]. Data from the PRiDe registry—using data from real-world recurrent GBM patients—also demonstrated improved OS with daily compliance rates  $\geq 75\%$  [23]. The results of the EF-14 sub-group analysis further support a threshold compliance rate of  $\geq 75\%$  for a survival benefit when compared to a compliance rate of <75% in newly diagnosed



GBM patients treated with TTFields plus TMZ. This study demonstrates that a minimal compliance threshold of > 50% with TTFields plus TMZ treatment correlated with significantly improved survival outcomes compared to TMZ alone for newly diagnosed GBM. TTFields were administered to GBM patients with recurrent disease as monotherapy in the EF-11 study and as combination therapy with TMZ in newly diagnosed GBM patients in the EF-14 study. The earlier disease stage and combined treatment may account for the survival benefits seen at a lower minimal compliance threshold in this subgroup analysis of the EF-14 study.

A variety of social and clinical factors contribute to patient compliance with TTFields therapy. Though TTFields are non-invasive and the Optune device is designed to preserve patient functioning during daily activities, initiating TTFields therapy requires some lifestyle modifications when compared to RT or systemic therapies. Some patients may be reluctant to comply with the head shaving required with every array change and wearing the arrays on a shaved head may make some patients self-consciousness, calling attention to their condition [28]. Healthcare providers experienced with TTFields therapy can provide patients assistance with incorporating the therapy in their daily life [28].

TTFields, like oral cancer treatment regimens, are administered in the home and outpatient setting and places the burden of compliance on the patient and their caregivers. Patient, healthcare provider, and treatment related factors can contribute to improved adherence or compliance with oral cancer therapy regimens [29]. Patient related factors include physical limitations, psychological, and social issues such as religious or cultural factors and the lack of a support system. The healthcare provider can also negatively influence compliance with therapy through poor communication and relationship with the patient, as well as failing to optimally select appropriate patients for oral cancer therapy regimens [29].

A good home support system is critical when considering TTFields therapy for a GBM patient [28]. A patient should have at least one support person who can assist with the Optune device operation, assist with managing adverse events, scalp maintenance and array placement. Patients with cognitive issues or poor performance status have been suggested to be more likely to be less compliant with TTFields treatment without home support [28]. However, the current study showed compliance to be independent of KPS and age as a predictor of PFS and OS, contradicting this suggestion. Treatment-related factors influencing compliance include complex treatment regimens, concomitant treatments and side effects. TTFields are not associated with systemic side effects and are less likely to affect concomitant systemic therapy.

The most common side effect in clinical trials was skin irritation for patients treated with TTFields [20, 24, 25].

Dermatological adverse events were the most common adverse events associated with TTFields; 52% of TTFields plus TMZ patients in the EF-14 trial reported mild to moderate skin irritation [24]. Skin irritation is due primarily to the nearly continuous contact of the transducer arrays with the patients shaved scalp between array changes. These events include allergic and irritant dermatitis, mechanical lesions, ulcers and skin lesions [30]. However, most of these dermatological AEs can either be prevented with proper shaving techniques, skin care and array relocations, or treated with appropriate topical regimens as required [30]. Effective skin care strategies can maximize compliance with TTFields therapy and maintain patient QoL over the course of treatment.

A limitation of this study is that it is based on a subgroup analysis of the phase 3 EF-14 trial, and inherently subgroup analyses are prone to type I errors limiting the veracity of the results [31]. In this instance, the subgroup analysis was prespecified in the protocol. However, the results of this investigation corroborate the results of similar analyses of prior clinical investigations [21–23].

## Conclusions

In this subset analysis of the EF-14 trial, a compliance threshold of 50% with TTFields plus TMZ treatment correlated with significantly improved outcomes compared to TMZ alone. Higher levels of treatment compliance with TTFields plus TMZ were associated with increased durations of progression free- and overall-survival suggesting a dose response mechanism for TTFields. This effect was independent of other prognostic factors such as performance status, age, and *MGMT* methylation status. Patients with compliance over 90% had a median survival of 24.9 months (28.7 months from diagnosis) and a 3-, 4-, and 5-year survival of 29.3%. This plateau effect on long term survival has been identified in other GBM treatments which have known immunologic mechanisms of action [32, 33]. The importance of compliance with TTFields therapy in real world clinical settings should be strongly conveyed to patients by their treating physicians and other allied healthcare providers.

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## Compliance with ethical standards

**Conflict of interest** S. A. Toms, C. Y. Kim and G. Nicholas have nothing to disclose. Z. Ram reports a research grant (principal investigator



and consultant) with Novocure, Ltd. and ownership interest (stock) in Novocure, Ltd.

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# CADTH ISSUES IN EMERGING HEALTH TECHNOLOGIES

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Alternating Electric Fields (“Tumour-Treating Fields”) for the Treatment of Glioblastoma



*Image courtesy of Novocure*



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## Summary

- Glioblastoma is the most common type of primary brain cancer in adults.
- Despite advances in treatment, life expectancy for patients with glioblastoma is typically less than two years.
- Optune is a wearable technology intended for use in addition to standard therapies — surgical resection, radiation therapy, and chemotherapy — in adults with either newly diagnosed or recurrent glioblastoma. It has also been trialled as a single therapy for adult patients with recurrent glioblastoma.
- Optune delivers alternating electric fields, or “tumour-treating fields,” to the brain to disrupt cancer cell division.
- The evidence suggests that some patients with newly diagnosed glioblastoma treated with Optune may live longer, although which patients are most likely to benefit is not yet entirely clear.
- The cost of therapy with the Optune system is about US\$21,000 per patient, per month.

## Background

Glioblastoma is also called glioblastoma multiforme (or GBM), Grade IV glioma, or Grade IV astrocytoma.<sup>1</sup> In adults, glioblastoma is the most common primary brain cancer (a cancer that originates in the brain).<sup>2,3</sup> Glioblastoma is difficult to treat because the cancer cells infiltrate normal brain tissue with tentacle-like extensions that usually cannot be completely removed surgically. Delivery of drug therapies to the tumour is also impeded by the blood-brain barrier (which protects the brain from harmful substances in the blood).<sup>4,5</sup> And because glioblastoma cancer cells are highly heterogeneous (that is, when they divide, the new cells are not genetically identical to the parent cells), new tumour growth can contain cancer cells that are resistant to treatment.<sup>4,5</sup>

With standard treatments, patients with glioblastoma have a median survival of about 15 months from the time they are diagnosed, and only one in four patients is alive at two years.<sup>4,6-11</sup> Glioblastoma typically recurs within about seven months of initial treatment.<sup>6,10</sup>

A wearable device that emits low-intensity, alternating electric fields is a new addition to treatment options for some patients with glioblastoma.

## The Technology

The Optune system (Novocure, St. Helier, Jersey Isle, UK), initially called NovoTTF-100A, was developed at the Technion – Israel Institute of Technology. It uses pre-set, low-intensity (one to three volts) alternating electrical fields at an intermediate frequency of 200 kHz to create “tumour-treating fields” (TTFields). These TTFields penetrate cell walls to disrupt rapid cancer cell division and cause cell death,<sup>12-14</sup> although the mechanism(s) of action are still not fully understood.<sup>15-17</sup> The TTFields treatment should be administered continuously, for at least 18 hours per day.<sup>14</sup>

The components of the Optune system include:

- four adhesive patches, called transducer arrays, that are worn on the patient’s head, with each array containing nine, insulated ceramic disks
- a connector cable
- a portable electric field generator
- four rechargeable battery packs (the system uses one battery at a time, each battery providing four to six hours of power)
- a customized backpack.<sup>18,19</sup>

The Optune system allows the patient to be mobile, using the battery pack and backpack, while receiving treatment, or the system can be plugged into a regular electrical outlet when the patient is seated or asleep.<sup>19</sup> It weighs about 1.3 kg, including the battery.<sup>18,20</sup>

Patients must shave their heads to allow the transducers to properly adhere to their scalp with a thin layer of conductive hydrogel similar to that used for electrocardiogram pads.<sup>19,21</sup> The transducer arrays are attached to adhesive bandages to hold them in place and are positioned in pairs on the head left and right, front and back.<sup>13,14</sup> Each transducer array is plugged into the connector cable, which is in turn plugged into the battery pack.<sup>19</sup> Replacement transducers are provided in sterile packages, and used transducers are returned to Novocure for disposal.<sup>1,19</sup> Ideally, the arrays are worn continuously for three to four days; but after exercise, or in hot or humid weather, more frequent exchanges may be needed.<sup>22</sup> The scalp must be shaved and cleansed before a new set of arrays can be applied.<sup>19,22</sup> Patients can wear a loosely fitting wig, scarf, or hat over the arrays, but the wires will still be visible.<sup>23</sup>

To help physicians identify the optimal placement location for the arrays on the patient’s head, the manufacturer provides the NovoTAL System software. This software uses data from the patient’s MRI scans to guide placement, and it can also be used to make adjustments to placement, as needed, throughout treatment.<sup>6,8</sup>



## Availability

The Optune system does not currently have a Health Canada Medical Devices Active Licence. However, the system has been used at Canadian hospitals in Ontario, Quebec, Manitoba, and Alberta as part of the multinational EF-14 trial.<sup>24</sup>

The US FDA first approved the Optune system in April 2011 for use in patients older than 22 years with recurrent glioblastoma, after standard medical therapies have been used.<sup>25</sup> In 2015, the FDA expanded the licensing to include the treatment of patients with newly diagnosed glioblastoma, after “maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.”<sup>25,26</sup> The Optune system is also commercially available in Europe, Israel, and Japan.<sup>26,27</sup>

## Cost

A 2016 report by the ECRI Institute notes that the cost of TTFields therapy is substantial — approximately US\$21,000 per patient each month.<sup>28</sup> The cost includes the Optune system, a month’s supply of transducer arrays, and 24-hour technical support.<sup>29</sup> The final EF-14 trial analysis showed the median duration of TTFields treatment was just over eight months.<sup>30</sup>

## Who Might Benefit?

Optune is intended for treatment of glioblastoma in the supratentorial (or upper) region of the brain, not for tumours in the cerebellum or brain stem.<sup>26</sup>

Glioblastoma is more common in older people, and is more common in men than in women.<sup>31</sup> Whereas primary glioblastoma most often affects older patients, secondary glioblastoma, which develops more slowly from a lower-grade glioma, usually occurs in younger patients.<sup>31</sup>

Precise numbers of Canadians with glioblastoma are not available, but based on estimates of the incidence of the disease from the US and Europe, approximately 1,200 Canadians may be diagnosed with glioblastoma each year.<sup>5,9,31</sup> The Brain Tumour Foundation of Canada’s Canadian Brain Tumour Registry is collecting information on the incidence and survival rates for all types of brain cancers, and more comprehensive data should be available within the next few years.<sup>32</sup>

## Current Practice

Patient care should be provided by a multidisciplinary team that includes specialists in neurosurgery, radiation oncology, neuropathology, neuro-oncology, and allied health.<sup>31</sup>

Standard treatment and management for glioblastoma include:

- surgical removal of as much of the tumour as possible while avoiding damage to critical areas of the brain, or biopsy only for inoperable tumours
- radiation therapy beginning three to six weeks after surgery and concurrent chemotherapy with oral temozolomide for three to six weeks
- subsequent maintenance temozolomide therapy for six cycles (or up to twelve months).<sup>4,9,11,31,33-35</sup>

Treatment may be modified for elderly or frail patients.<sup>34</sup>

## Methods

These bulletins are not systematic reviews and do not involve a detailed critical appraisal. They are not intended to provide recommendations for or against a particular technology.

## Study Selection

One author screened the literature search results and reviewed the full text of all potentially relevant studies. Studies were considered for inclusion if the intervention included alternating electric fields for glioblastoma. Conference abstracts and grey literature were included when they provided additional information to that available in the published studies.

## Peer Review

A draft bulletin was reviewed by two clinical experts and the manufacturer.

## Literature Search Strategy

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, Embase, PubMed, and the Cochrane Library (2017, Issue 6). Grey literature was identified by searching relevant sections of the *Grey Matters* checklist (<https://www.cadth.ca/grey-matters>). No methodological filters were applied. The search was limited to English-language documents published between January 1, 2012 and May 30, 2017. Regular alerts updated the search until project completion; only citations retrieved before December 19, 2017 were incorporated into the analysis. Conference abstracts were retrieved through a search of the Embase database limited to the last two years.



Prognosis is affected by the patient's age, Karnofsky Performance Status (which measures functional ability or disability), the amount of tumour that can be surgically removed, and the molecular features of the glioblastoma, such as genetic alterations associated with a better or worse response to temozolomide chemotherapy.<sup>4,31</sup>

Other drug therapies may be used to treat disease recurrence, but evidence that they improve survival is still not conclusive, and they may cause serious adverse events.<sup>31,36,37</sup>

The 2016 US National Comprehensive Cancer Network consensus-based guidelines include "lower-level" evidence recommendations for alternating electric fields therapy as an add-on treatment option to standard therapy for newly diagnosed patients with glioblastoma in the supratentorial region of the brain; and as a treatment option for patients with recurrent glioblastoma.<sup>3</sup>

## The Evidence

Optune has been assessed in several clinical trials over the past decade;<sup>13</sup> the most recent evidence includes two randomized controlled trials (EF-14<sup>30,38</sup> and EF-11<sup>39</sup>) and the PRiDe Patient Registry Dataset.<sup>40</sup>

In the remainder of this section, the trials and the registry study are described first, followed by summaries of the main outcomes: overall survival, progression-free survival, compliance, quality-of-life, and safety. Smaller case series and subgroup analyses are also noted under the relevant outcomes sections.

Some trials included patients newly diagnosed with glioblastoma,<sup>30,38</sup> whereas others included patients at first, second, or later recurrence of cancer.<sup>39</sup> Consequently, the timing and duration of TTFields treatment varied.<sup>6,17</sup> The drug therapies used in the trials also differed; for example, the use of temozolomide alone, or the use of triple therapy that included temozolomide and/or other drugs.<sup>30,38-40</sup> The trials did not use a sham treatment in the control group, as it was considered impractical and inappropriate to place an additional burden on patients and caregivers (for example, shaving the patient's head and placement of the transducer arrays).<sup>16,30,38</sup>

Most publications on Optune — including studies, reviews, and commentaries — received funding from the manufacturer.<sup>6-9,11,13,14,18,19,21,22,30,38-67</sup>

## Study Characteristics

### EF-14

Interim results from the EF-14 trial — the largest, multinational trial of TTFields therapy — were published in 2015,<sup>38</sup> and the

final study results were published in December 2017.<sup>30</sup> The trial involved 695 patients at 83 centres. Patients were all newly diagnosed with glioblastoma and had all received standard treatment: debulking surgery (to reduce the size of the tumour), where feasible; radiation therapy; and chemotherapy. Participants were randomized at a ratio of 2 to 1 to receive maintenance therapy with either TTFields plus temozolomide (466 patients), or temozolomide only (229 patients). Patients in either group who experienced cancer progression could also receive second-line chemotherapy. Patients in the TTFields group who experienced cancer progression could continue to receive TTFields treatment. The trial excluded patients with disease progression prior to randomization. Patients who were not able to complete primary treatment and those who could not tolerate temozolomide chemotherapy were also excluded.

The interim analysis of EF-14 trial data was planned to occur when there was at least 18 months of follow-up for the first 315 randomized patients: 210 in the TTFields group, and 105 in the temozolomide-only group.<sup>38</sup> Based on the positive interim results, the trial's data and safety monitoring committee recommended stopping the trial, and TTFields therapy was offered to all patients.

Participants in the EF-14 trial were followed for a median of 40 months and a minimum of 24 months.<sup>30</sup>

### EF-11

In the EF-11 trial, published in 2012, 237 patients with recurrent glioblastoma were randomized to receive either TTFields therapy only (n = 120) or the physician's choice of chemotherapy (n = 117).<sup>39</sup> To be included, patients must have received prior radiation therapy, with or without temozolomide chemotherapy. Patients with implanted medical devices, such as pacemakers, were excluded. Most patients were at the second or third recurrence of the disease. Their assigned treatment began within one week of randomization and continued until their disease progressed further or they were found to be unable to tolerate their assigned treatment. The trial was conducted at 28 centres in the US, Europe, and Israel.<sup>39</sup>

### PRiDe

The Patient Registry Dataset (PRiDe) is a post-marketing registry study following 457 patients with recurrent glioblastoma who received the TTFields therapy in 91 US centres between October 2011 and November 2013.<sup>40</sup> The intent was to gather real-world clinical practice information on patients treated with TTFields. The patients in the registry could have received any prior therapies and could have had any number of cancer recurrences. The median duration of TTField treatment in the registry patients was 4.1 months.<sup>40</sup>



## Overall Survival

In the final analysis of the EF-14 trial, the median overall survival in the intention-to-treat patient groups was 20.9 months in the TTFields-plus-temozolomide group, and 16.0 months in the temozolomide-only group.<sup>30</sup> More than half of the patients in both treatment groups also received second-line drug therapies: 67% of patients in the TTFields-plus-temozolomide group and 57% of those in the temozolomide-only group.<sup>38</sup> At two years after trial enrolment, more of the patients in the TTFields-plus-temozolomide group were alive (43%) compared with the temozolomide-only group (31%).<sup>30</sup>

In the EF-11 trial of patients with disease recurrence, there was no difference in overall survival between the TTFields-only group and the chemotherapy-only group at any time point.<sup>39</sup> Investigators concluded that the EF-11 trial showed that TTFields treatment offered comparable efficacy to that achieved with chemotherapy.<sup>59</sup>

**“In the final analysis of the EF-14 trial, the median overall survival in the intention-to-treat patient groups was 20.9 months in the TTFields-plus-temozolomide group, and 16.0 months in the temozolomide-only group.”**

Authors of the PRiDe registry study also conducted an analysis of survival. Median overall survival was 9.6 months.<sup>40</sup> At one year, 44% of registry patients were alive, and at two years, 30% of patients were alive.<sup>40</sup>

A post-hoc analysis of the EF-11 trial found that median overall survival was higher in patients with recurrent glioblastoma who used the TTFields device for 18 or more hours daily (survival rate of 7.7 months) compared with patients who used the system less (survival rate of 4.5 months).<sup>47</sup>

Researchers at one US centre reported on a small case series that found improved survival in patients who received TTFields treatment in addition to triple-drug therapy (temozolomide, bevacizumab, and irinotecan).<sup>68</sup> Median overall survival was 34.5 months for the 29 patients who received the combined treatment, and was slightly longer — 39.4 months — for the 15 patients who started TTFields treatment earlier (i.e., within 125 days of initial diagnosis).<sup>68</sup>

Another small study, reported in a conference abstract, found that the median overall survival was 12 months in 12 patients who received stereotactic radiosurgery in addition to TTFields therapy,

compared with four months in 28 patients who received TTFields therapy without radiosurgery.<sup>67</sup>

A small case series of eight patients with bevacizumab-refractory glioblastoma reported a median overall survival of 7.2 months from the start of TTFields therapy.<sup>41</sup> Several case reports mention long-term survivors of glioblastoma who have either continued to use TTFields therapy for several years (in addition to drug and other treatments),<sup>12,47,55,69</sup> or who have been in good health and are no longer receiving treatment after receiving TTFields treatment.<sup>47,49,56,70</sup>

## Progression-Free Survival

Progression-free survival is the period of time during and after treatment in which the disease does not worsen. Final EF-14 trial results reported that median progression-free survival in the intention-to-treat patient groups was 6.7 months in the TTFields-plus-temozolomide group, and 4.0 months in the temozolomide-only group.<sup>30</sup>

There was no difference in median progression-free survival at six months in the EF-11 trial patients with recurrent glioblastoma (just over two months in both the TTFields-only group and the chemotherapy-only group).<sup>39</sup>

## Compliance With Treatment

The use of TTFields for 18 or more hours per day is associated with better overall survival.<sup>6,7,30,47,71</sup> At least one continuous 28-day cycle of TTFields treatment is necessary to be able to see a treatment effect (usually based on MRI imaging, if available).<sup>47,48</sup> The Optune system records the amount of time the patient uses the device in a monthly report for the attending physician.<sup>18</sup>

In the EF-14 trial, 75% of the patients in the TTFields-plus-temozolomide group wore the device for an average of 18 or more hours per day.<sup>30</sup>

In the EF-11 trial, of the 116 patients who started TTFields treatment, 78% completed at least one four-week cycle.<sup>39</sup> The average compliance with treatment was 86% (an average of 20.6 hours per day).<sup>39</sup> Twenty-seven patients stopped TTFields treatment early, either because of not using the system for the recommended hours each day or because of an inability to manage the device.<sup>39</sup>

PRiDe registry compliance data were available for only about two-thirds of the patients (n = 287).<sup>40</sup> About 44% of the patients (n = 127) used the TTFields therapy for 18 or more hours per day. Patients with more functional impairment were less compliant in their use of the TTFields treatment.<sup>40</sup>

A small case series of patients with bevacizumab-refractory glioblastoma reported a compliance rate of 74.2%; this was based



on seven of the eight patients' records, with a median duration of TTFields therapy of 5.2 months.<sup>41</sup>

## Quality of Life

Interim EF-14 trial results showed an initial improvement in quality of life in the patients treated with TTFields plus temozolomide, but at the nine-month follow-up there was no difference between the patient groups.<sup>43</sup> Self-reported physical and social functioning were also similar between the groups at the nine-month and the 12-month follow-up.<sup>43</sup> Final EF-14 study results on quality of life are forthcoming.<sup>30</sup>

Data on quality of life was available for 63 patients (27%) in the EF-11 trial who remained on TTFields therapy for at least three months.<sup>39</sup> These patients reported a higher quality of life — including better cognitive and emotional status — than those in the chemotherapy group, possibly because they were not experiencing the toxic effects of chemotherapy.<sup>11</sup> There was no difference between the groups in the domains of overall health and social functioning.<sup>39</sup>

## Safety

### Skin Irritation

The most common adverse event with the use of TTFields therapy is skin irritation, including rash, ulceration, and infections.<sup>19,21,72</sup>

The irritation is mainly due to repeated shaving of the scalp, application and removal of the transducer arrays, allergic reaction to the hydrogel, and the pressure of the transducers on the skin.<sup>14,19</sup> Skin irritation was usually mild to moderate, and it was treatable with topical steroids or antibiotics and by slightly adjusting the positioning of the transducer arrays and adhesives when they were exchanged. It was also treated by removing the arrays for a few days.<sup>19,72</sup>

In the EF-14 trial, about 52% of patients in the TTFields group had mild to moderate skin reactions, and about 2% of patients had more severe skin reactions.<sup>30</sup> Patients in the TTFields-plus-temozolomide treatment group reported "itchy skin" more often than those in the temozolomide-only group.<sup>43</sup> In the EF-11 trial, 16% of patients in the TTFields group experienced mild to moderate skin irritation.<sup>39</sup>

In the PRiDe registry, 24.3% of patients (the actual patient numbers were not reported) experienced skin reactions.<sup>40</sup> Although some patients reported a sensation of scalp warmth, this did not cause injury.<sup>40</sup> (When the device is in operation, sensors in the arrays monitor temperature. The system sounds an alarm and automatically shuts off if the temperature rises above 105.8°F or 41°C.<sup>19</sup>)

## Systemic Adverse Events

In the EF-14 trial, systemic adverse events such as blood and gastrointestinal disorders, seizures, and infections were similar in the patients who received TTFields plus temozolomide, and those who received temozolomide only.<sup>30</sup> In the EF-11 trial, systemic adverse events such as gastrointestinal and blood disorders, and infections, occurred more frequently in the chemotherapy patient group.<sup>39</sup>

A post hoc analysis of 144 patients in the EF-14 trial who received TTFields in addition to second-line drug therapies after disease recurrence found a higher incidence of adverse events compared with patients who received chemotherapy only.<sup>51</sup> These results may have been confounded by the second-line drug therapies used (most commonly bevacizumab), the longer follow-up period for patients who received TTFields, and the 14 patients who crossed over to the TTFields treatment arm who had not initially received TTFields.<sup>51</sup>

**"The most common adverse event with the use of TTFields therapy is skin irritation, including rash, ulceration, and infections."**

### Other Adverse Events

Other adverse events reported in the registry patients included neurological disorder (10.4%), seizure (8.9%), headache (5.7%), pain or discomfort (4.7%), and falls (3.9%). Actual patient numbers were not reported.<sup>40</sup>

In the EF-14 study, the rates of seizures were similar in the patients who received TTFields plus temozolomide and those who received temozolomide only.<sup>30</sup>

TTFields therapy should not be used in patients with active implanted devices — such as deep brain, spinal cord, or vagal nerve stimulators; or pacemakers — or in individuals with a sensitivity to the conductive hydrogels.<sup>25,26,61</sup> A 2017 laboratory study concluded that radiation therapy should not be used when the transducer arrays are in place because of an increased risk of skin toxicity.<sup>50</sup>

## Cost Studies

No Canadian economic evaluations were identified.

French researchers examined the cost-effectiveness of TTFields therapy in patients newly diagnosed with glioblastoma based on interim data from the EF-14 trial.<sup>29</sup> Two scenarios were considered: the first, standard of care alone, which included radiation therapy and temozolomide; and the second, TTFields treatment plus standard of care. With a projected life expectancy



of 22.08 months in the TTFields scenario and 18 months in the standard of care alone scenario, TTFields therapy costs €243,141 compared with €57,665 for standard treatment alone; with an incremental cost-effectiveness ratio (ICER) of €549,909 per life-year gained.<sup>29</sup> A Swedish cost-effectiveness evaluation using more recent patient data has also been conducted; however, the results are not available in English.<sup>73</sup>

A systematic review of economic studies assessing the cost-effectiveness of glioblastoma therapies, including TTFields therapy, is underway at the University of York and expected to be published in 2018.<sup>74</sup>

## Concurrent Developments

### Treatments for Glioblastoma

Molecular-based tumour typing is increasingly important in cancer diagnosis and treatment decisions.<sup>75,76</sup> People with glioblastoma tumours that have particular genetic alterations have better prognoses than those with tumours having only some or none of these alterations.<sup>75</sup>

Many clinical trials for glioblastoma therapies are in various phases of development.<sup>77-79</sup> Some researchers have speculated there may be a synergistic effect between TTFields therapy and the response to drug therapies.<sup>42,57,62</sup> Clinical trials of TTFields therapy in combination with other therapies are also in progress.<sup>8,17,80</sup>

Immunotherapies, vaccines, and oncologic viruses that promote the patient's immune system response or target tumour cells are other areas of investigation.<sup>76,77,81-83</sup> Glioblastoma is one of the cancers included in chimeric antigen receptor (CAR) T-cell therapy research — where a patient's T-cells are extracted, genetically modified, and reinfused to attack cancer cells.<sup>78,84,85</sup>

Ultrasound technologies, such as microbubbles that temporarily allow better access of drug therapies across the blood-brain barrier, and focused ultrasound ablation (or removal) of tumours have also been investigated in the treatment of glioblastoma.<sup>5,86,87</sup>

Another device-based treatment for glioblastoma is the Nativis Voyager (Nativis, Seattle), which is undergoing feasibility and safety trials in the US and Australia.<sup>88,89</sup> The Nativis Voyager is worn on a headband and the device delivers ultra-low radiofrequency energy to the brain. The radiofrequency energy is believed to disrupt genetic processes in the cancer cells — in particular, the epidermal growth factor receptor — and prevent cell division.<sup>89</sup>

### Other Uses of Tumour-Treating Fields

Small studies of TTFields in treating other types of cancers have also been published or are underway, including investigations of its use in meningioma — a brain tumour that forms on the membranes covering the brain and spinal cord; brain metastases from other types of cancer; mesothelioma (a rare cancer related to asbestos exposure); and pancreatic, lung, and ovarian cancers.<sup>8,11,13,17,36</sup> A Danish trial is investigating the feasibility of increasing TTField intensity to the tumour by craniectomy — removing small pieces of the overlying skull.<sup>52</sup>

A report of compassionate use of TTFields treatment in five children and adolescents with high grade gliomas (including glioblastoma) concluded a pediatric trial would be worthwhile,<sup>90</sup> and the Pediatric Brain Tumor Consortium is conducting a trial in children.<sup>91</sup>

## Implementation Issues

### Uptake

A 2017 US review noted that uptake of TTFields treatment has been relatively slow, and that only about 15% of patients newly diagnosed with glioblastoma were treated with TTFields in 2016.<sup>7</sup> Worldwide, over 5,000 patients with glioblastoma have been treated with TTFields (Justin Kelly, Novocure, Portsmouth, NH: personal communication, 2017 Oct 30).

### Training Needs

Originally, Novocure clinical staff customized the layout of the transducer arrays for each patient.<sup>92</sup> Now, physicians who prescribe Optune must receive training and certification to do this for their patients using the NovoTAL System.<sup>33,92,93</sup> A study involving 14 physicians (neuro-oncologists, medical oncologists, and neurosurgeons) certified to prescribe Optune found that physicians in all specialties were able to use the system to accurately initiate and adjust patient treatment.<sup>92</sup>

Patients and their families or caregivers also need training in using the device and in scalp preparation, and in ensuring the correct placement of the transducer arrays.<sup>1,7,14</sup>

### Caregiver Burden

Cleansing and shaving the scalp, replacing the electrodes every three days, and wearing the device for most of the day and night may be a burden for some patients.<sup>7</sup> Most patients will need help to prepare their scalp and apply the arrays, and family or caregiver support will likely be needed.<sup>7,22,59</sup>



## Patient Perspective

The need to shave the head and wear the noticeable transducer arrays and wires may be seen as a stigma of cancer, as with hair loss in chemotherapy.<sup>7,16,63,65,94</sup>

Jeffrey Weiss, a US journalist with glioblastoma who has since passed away, chronicled his experience as a patient with this disease, including his experience using the TTFields therapy:

"Optune use is a real-world physical hassle. Four palm-sized patches of electrodes are stuck to my scalp in a particular pattern. Every two days, the electrodes must be removed, my scalp cleaned and reshaved, and a new set of electrodes stuck on. (My wife, Marni, has to do the electrode installation; I can't possibly reach all around my head to get them on correctly.) Sweat is a problem. It can make the electrodes fall off. Heat is a problem; if my head gets even a bit warm, an alarm goes off. When I leave the house, I wear hats to cover the odd-looking electrode patches..."<sup>95,96</sup>

One investigator with the EF-14 study noted that patients:

"...became psychologically dependent on the TTFields device, and saw it as a tangible way to treat their own disease. They were responsible for wearing the device, taking it with them throughout the day, and recharging the batteries. They also had to change their transducer arrays every few days..."<sup>61</sup>

This is in contrast to other cancer treatments where patients are more passive recipients of care.<sup>22,61</sup> As one US patient who has used the system for two years said: "I wear it and wear it proudly... It's an incredible machine and I'm fine not having hair."<sup>97</sup>

Some patients found the system cumbersome, but future design modifications are expected.<sup>8,62</sup> A 2016 conference abstract, reporting one centre's experience with providing TTFields therapy, described the following reasons patients gave for not using the system: inability to tolerate the side effects (not specified), lack of caregiver support, and impact on lifestyle.<sup>98</sup> In addition, two patients did not start TTFields therapy as prescribed because of social or financial reasons.<sup>98</sup>

## Patient Education

Health care providers will need to educate patients and their families about the importance of compliance, as the effectiveness of TTFields depends on the device being worn and turned on.<sup>7,22,47</sup> A recent guide for nursing staff noted that some patients experience cognitive impairment as a result of their disease treatments, so that user errors — such as not noticing the device was not turned back on after a break in therapy — may occur, which can affect compliance.<sup>22</sup> The device's compliance report

for physicians may help to identify these types of issues.<sup>22</sup> In addition to supporting the health care professionals, Novocure technicians are available to provide technical support to patients and caregivers.<sup>22</sup>

## Patient Selection

It is not yet clear which patients with glioblastoma are most likely to benefit from TTFields treatment.<sup>16,17</sup> The distribution of the electrical fields to the tumour is affected by many variables in addition to the positioning of the transducer arrays, including the location and shape of the tumour and whether it contains a core of necrotic (or dead) tissue, the layer of cerebrospinal fluid, and the insulating properties of adjacent tissue.<sup>99</sup>

**"The cost of TTFields therapy will be a barrier for patients if this therapy is not covered by public and private health insurance."**

Preliminary evidence suggests that patients who may benefit most are those:

- with tumours that are more superficial, rather than those located deep within the brain.<sup>100</sup>
- who have not previously received bevacizumab. These patients may have a better prognosis.<sup>40,64</sup> However, a small subgroup analysis also suggested that patients who have developed resistance to bevacizumab may have a better response to TTFields therapy — possibly because of an altered immune response after receiving bevacizumab.<sup>47</sup>
- with tumours that developed from lower grade gliomas. These tumours appear to have a better response to TTFields therapy.<sup>45</sup> As primary and secondary glioblastomas differ genetically, in the future, the genetic profiling of tumours may allow for better identification of patients who will benefit from TTFields treatment.<sup>45</sup>

## Imaging Needs

Planning the patient's transducer array layout is based on existing MRI imaging taken as part of standard care for glioblastoma (Justin Kelly, Novocure, Portsmouth, NH: personal communication, 2017 Oct 30). Subsequent MRIs, every two to three months, are also part of standard follow-up for patients with glioblastoma.<sup>14</sup> For a more accurate assessment of treatment response in glioblastoma, investigators are exploring advanced MRI-based techniques, such as diffusion tensor imaging, 3-D echo-planar spectroscopy, and dynamic susceptibility contrast perfusion-weighted imaging.<sup>54,101</sup>



## Pseudoprogression

In patients with glioblastoma, pseudoprogression (transient visual changes in the tumour not indicative of true disease progression), commonly due to tissue necrosis from radiation therapy, is often seen on follow-up MRIs within the first months after chemotherapy and radiation treatment.<sup>14,31,102</sup> There is also a delay between treatment response with TTFields and when this becomes evident on MRI images.<sup>14</sup> Continuation of TTFields treatment is recommended, regardless of early diagnostic imaging results.<sup>7,48,49,70,93</sup> The effects of a prolonged use of TTFields after cancer recurrence — for example, on slowing the rate of progression or on tumour regression — warrant further investigation.<sup>16</sup>

## Other Issues

The cost of TTFields therapy will be a barrier for patients if this therapy is not covered by public and private health insurance.<sup>7,23</sup>

The reduced incidence of systemic adverse events with TTFields therapy for patients with recurrent glioblastoma may reduce health care costs associated with treating more serious adverse events caused by chemotherapy and radiation therapy.<sup>8</sup> A 2012 Australian health technology assessment of TTFields therapy included unpublished manufacturer's information that found fewer hospitalizations and reduced length of stay among the patients who received TTFields treatment compared with those who received best standard chemotherapy.<sup>103</sup>

In the US, the Novocure support technicians meet with patients each month to provide support and download the compliance report for the health care team.<sup>22</sup> How this works for patients outside of the US is not clear.

## Final Remarks

In September 2017, Novocure announced that the German Federal Joint Committee, the Gemeinsamer Bundesausschuss, will jointly fund a new trial to assess the benefit of starting TTFields treatment earlier — as part of initial therapy alongside radiation therapy and temozolomide.<sup>104</sup>

Treatments that may improve survival without negatively affecting quality of life are important for patients with this aggressive, difficult-to-treat cancer.<sup>43</sup> Nevertheless, some clinicians remain skeptical about the benefits of TTFields — perhaps because it is so different from traditional cancer treatments.<sup>7,16,23,63</sup> Further research is underway that may clarify the place of TTFields in the treatment of glioblastoma.



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# A review on Tumor Treating Fields (TTFields): Clinical implications inferred from computational modeling

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**Abstract**—Tumor Treating Fields (TTFields) are a cancer treatment modality that uses alternating electric fields of intermediate frequency (~100-500 kHz) and low intensity (1-3 V/cm) to disrupt cell division. TTFields are delivered by transducer arrays placed on the skin close to the tumor and act regionally and non-invasively to inhibit tumor growth. TTFields therapy is FDA approved for the treatment of glioblastoma multiforme, the most common and aggressive primary human brain cancer. Clinical trials testing the safety and efficacy of TTFields for other solid tumor types are underway.

The objective of this article is to review computational approaches used to characterize TTFields. The review covers studies of the macroscopic spatial distribution of TTFields generated in the human head, and of the microscopic field distribution in tumor cells. In addition, pre-clinical and clinical findings related to TTFields and principles of its operation are summarized. Particular emphasis is put on outlining the potential clinical value inferred from computational modeling.

**Index Terms**—Computational Modeling and Simulation, Finite Element Models, Cancer Treatment, Tumor Treating Fields

## I. INTRODUCTION

### A. Electric field interactions with biological tissue

It is well established that electric fields (EFs) affect cellular function. Direct current or low-frequency alternating fields (<1 kHz) affect the polarization of cell membranes [1] and induce excitatory or inhibitory effects on electrically excitable tissue. Thus, medical applications utilizing low frequency fields target a multitude of diseases in a range of tissues including neural and muscle tissue [1]. High frequency fields

(MHz range) do not induce membrane polarization but rather cause fast oscillation of polar molecules (friction) [2] leading to tissue heating. Therefore high frequency electromagnetic fields are used for applications, such as diathermy and tissue and tumor ablation [3]. Until recently the intermediate frequency range of several hundred kHz had not been considered for medical applications, since currents in this range alternate too fast to stimulate nerves or muscles and induce only minute heating through ohmic and dielectric loss [4]. However, since the early 2000's, several studies have shown that intermediate frequency fields disrupt cell division in cancer cells [5], [6]. These observations have led to the development of Tumor Treating Fields (TTFields) [5], [6], a physical modality for treating cancer.

### B. TTFields: pre-clinical observations and mechanisms of action

TTFields are alternating EFs in the frequency range of 100-500 kHz and intensities typically in the range 1-3 V/cm [5] that exert an anti-mitotic effect on cells. TTFields have been studied *in vitro* using several preclinical laboratory research systems that have been developed for this purpose. These systems include, the Inovitro™ system (Novocure Ltd.), [7] which consists of a TTFields generator connected to a set of ceramic petri dishes, microfluidic devices [8] and wire based devices [5], [9], [10]. Using these types of devices, researchers have shown that exposing cells to TTFields leads to prolonged mitosis, the formation of abnormal mitotic figures and mitotic cell death [5], [11], [12]. TTFields also induce violent membrane blebbing during telophase, which in turn leads to the formation of abnormal daughter cells and induction of cell death in the following interphase [5], [13]. The anti-mitotic effect of TTFields is synergistic with the effects of chemotherapeutic agents [14]–[16]. When combined with TTFields, chemotherapeutic agents delivered at doses well below the therapeutic threshold lead to complete cell cycle arrest [14]. Pavesi et al. (2016) showed that TTFields application leads to reduced proliferation of breast cancer cells, whilst leaving normal human endothelial cells largely unaffected [8]. Recent studies have also demonstrated that TTFields can inhibit cell migration [9] and DNA damage repair [10], [17].

TTFields effect is intensity dependent. Cell growth rate decreases as field intensity increases. For most cell lines, growth rates begin to decrease when the field intensity

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exceeds a threshold of about 1 V/cm, and growth is completely arrested when field intensity exceeds about 2.5 V/cm [5], [6]. The effect is also frequency dependent, and each cell line has an optimum frequency, at which the inhibitory effect on cell growth is most significant [5], [6]. For glioma cells the optimal frequency is 200 kHz [5], [6]. In addition, cells dividing parallel to the field are more likely to be affected by the field than cells dividing in other directions [6], and periodically switching the field between two orthogonal field directions was shown to be 20% more effective compared to applying TTFIELDS in a single direction [6]. Finally, cells with a short doubling time are more susceptible to the effect TTFIELDS [12], likely due to the higher frequency of mitotic events in a given time.

It has been proposed that TTFIELDS exert their effect by causing alignment of proteins with large dipole moments with the EF [5], [6], thereby disrupting structures and inhibiting protein polymerization. Indeed, two proteins with large dipole moments, tubulin dimers (1740 Debye – [18]) and septin (2711 Debye–[13]) are affected by TTFIELDS. Studies show that TTFIELDS disrupt microtubule (MT) polymerization, preventing proper chromosome segregation during mitosis [12], and that under the influence of TTFIELDS, septin, which serves as scaffold for the actin myosin ring closing the cytokinetic furrow, fails to localize to the cell mid-zone leading to ectopic blebbing and abnormal mitosis [13].

To explain the effect of TTFIELDS, it has also been suggested that when TTFIELDS are applied to cells during telophase, the hourglass shape of the dividing cell causes the EF within the cell to become highly non-uniform with higher field intensities close to the narrow furrow region. Such field inhomogeneity results in dielectrophoretic (DEP) forces [19] possibly leading to irregular aggregation of polarizable particles, thereby disrupting cell division [4], [5].

These two theories were recently evaluated in a theoretical analysis by Tuszyński et al. [20]. According to this analysis, the DEP forces that develop during telophase are indeed strong enough to interfere with mitosis. However, the forces and torques that the EF exerts on the intrinsic dipoles of tubulin are too small to have a significant effect on tubulin alignment. This analysis demonstrates that although the biological effects of TTFIELDS on cells are well-documented, there is still a need for in-depth biophysical studies to elucidate the physical mechanisms by which TTFIELDS exert their biological effects [21].

### C. TTFIELDS: clinical trial and clinical settings

The clinical application of TTFIELDS has been tested in animal models [5]–[7], [11], [22], [23] and several clinical trials, the first of which demonstrated that exposure to TTFIELDS led to local regression of skin metastases from breast cancer and melanoma [24]. A pilot trial with patients suffering from glioblastoma multiforme (GBM) showed that treatment with TTFIELDS is feasible and well tolerated without causing serious adverse effects [25]. A subsequent phase III clinical trial (EF-11) compared the efficacy of TTFIELDS to the physician's best choice of chemotherapy in recurrent GBM

patients [26]. This trial showed comparable efficacy between the two arms with a better quality of life and less toxicity for TTFIELDS patients [26] leading to the US Food and Drug Administration (FDA) approving TTFIELDS for the treatment of recurrent GBM in 2011. The subsequent EF-14 trial showed that treating newly diagnosed GBM patients with a combination of TTFIELDS and temozolomide led to a 5 month increase in median overall survival (hazard ratio 0.65,  $p < 0.00005$ ) relative to patients treated with temozolomide alone [27]–[29]. TTFIELDS combined with temozolomide was approved by the FDA for the treatment of newly diagnosed GBM in October 2015.

Clinical trials testing feasibility and safety and/or efficacy of applying TTFIELDS to non-small cell lung cancer (Lunar – [30], [31]), pancreatic (Panova – NCT01971281 [32]), ovarian cancer (Innovate - NCT02244502), mesothelioma (Stellar-NCT02397928), and brain metastasis (Metis - NCT02831959, Comet - NCT01755624) have also been initiated.

When treating GBM, TTFIELDS are delivered using the Optune™ system (Novocure Ltd). The system weighs 1.3 kilograms and comprises a portable battery powered field generator, which is connected to two pairs of transducer arrays placed on the shaved scalp of the patient. One pair of arrays is placed on the left and right sides of the head (LR array), and the other pair on the anterior and posterior aspects of the head (AP array). Each array consists of 9 ceramic disks arranged in a 3x3 configuration [33]. The device delivers a maximum current of 2000 mA peak-to-peak at a frequency of 200 kHz. At any given instance, the current is delivered to only one pair of arrays, and the direction of the field is switched between the pairs of arrays once per second. Patients are treated outside the hospital environment and advised to wear the device for a minimum of 18 hours per day to ensure effective treatment [33]. The transducer arrays are disposable and replaced every few days [33], [34]. The same principles apply to treatment of other body regions, with the frequency of the field and the geometry and positioning of the transducer arrays adapted for each application. For instance, in clinical trials, lung cancer is treated using the NovoTTF-100L™ device, which delivers TTFIELDS at 150 kHz and is configured with larger transducer arrays than the Optune device [31], [35].

The placement of Optune™ transducer arrays on the patient's scalp (referred to as layout) is determined using the NovoTAL™ system [36], [37]. NovoTAL™ uses measurements of the head and tumor obtained from axial and coronal MR images of the patient to derive array layouts that maximize the field delivery to the tumor. Treatment planning with NovoTAL™ was defined as part of the protocol for the EF-14 trial, and is standard when initiating TTFIELDS treatment [36]. Computational studies have shown increased EF delivery to the diseased region [38], [39] when arrays are adapted to the individual tumor location.

### D. Article motivation and purpose

Many factors are known to influence the outcome of GBM treatment. These factors include: age, Karnofsky performance status (KPS), the extent of the resection, and morphological,



histological and genetic characteristics, such as IDH and MGMT tumor mutation status [40], [41]. When treating with TTFields, it is reasonable to assume that in addition to the factors mentioned above [21], the distribution and intensity of the induced EF in the brain and tumor also influence treatment outcome. The field distribution and intensity may vary significantly between individuals depending on the size, shape and electrical properties of the head, brain and tumor. It would be highly desirable to measure the field intensities in the regions of interest. However presently this task remains challenging. Hence, numerical simulations are the best available tool for evaluating TTFields distributions within patients.

In this paper we will review computational studies analyzing the application of TTFields. We will show how modelling TTFields at the cellular level can be used to investigate the biophysical basis for TTFields mechanisms of action, and how realistic human head models can be used to investigate the connection between EF distribution and efficacy and safety of TTFields treatment. We will discuss how, in the future, these models could be employed to study treatment response, predict progression patterns, conduct retrospective outcome analysis, enable prospective personalized treatment planning, and possibly help to select suitable candidates for therapy

## II. COMPUTATIONAL MODELS OF TTFIELDS

Whether simulating TTFields delivery at the cellular scale (section 2.1) or at the full head scale (section 2.2), the EF distribution is approximated by applying volume conductor models [1] to numerically solve derivatives of Maxwell's equations of electrodynamics with appropriate boundary conditions (BCs). For TTFields, the electromagnetic wavelength is much larger than the size of the models, and therefore the electro-quasistatic approximation of Maxwell's equations may be applied [42]. Thus, the electric potential  $V$  can be found by solving the Laplace equation,  $\nabla \cdot \tilde{\sigma} \nabla V = 0$ . Here  $\tilde{\sigma} = \sigma + i\omega\epsilon$  is the complex conductivity  $\epsilon$  is the permittivity,  $\sigma$  the electrical conductivity and  $i$  the imaginary unit, and  $\omega = 2\pi f$  the angular frequency. The numerical task of solving the Laplace equation can be achieved using for example, the finite element (FE) method. Table 1 illustrates the similarities and differences between cellular scale and full head scale models for studying TTFields.

### A. Cellular level modeling

#### 1) Materials & Methods

Glioma cells have been found to round up during mitosis to a sphere of approximately 5500 fL (radius of approximately 11  $\mu\text{m}$ ) [43]. According to images of the division process [43], as the cell proceeds into telophase elliptical cell shapes with equal size become more appropriate to characterize the process in which the daughter cells form.

To reflect these geometries, studies simulating TTFields application to single cells [20], [44]–[46] assumed a spherical cell with a default radius of 10  $\mu\text{m}$  during metaphase. During

TABLE I  
COMPUTATIONAL MODELING OF TTFIELDS APPLICATION

	Cellular level model	Human head model
purpose	study of TTFields mechanism of action	study of TTFields clinical application
related device	Inovitro™	Optune™
model creation	simple geometric objects	MRI tissue segmentation
model physics	electro-quasistatic approximation of Maxwell's equations	electro-quasistatic approximation of Maxwell's equations
model result	EF distribution in the extracellular space, the cell membrane, and cytosol	EF distribution in the head and tumor tissues

telophase and cytokinesis, elliptical sister cells with a default major radius of 10  $\mu\text{m}$  and minor radius of 7  $\mu\text{m}$  were considered. Three different stages of telophase were modelled by decreasing the length of the incision plane between the sister cells (furrow length) as division progressed (red line in bottom panel of Fig.1).

The models comprised three domains: the extracellular space, the cytosol and the membrane, which differ in their dielectric properties. The standard values assigned to these tissue types were:  $\sigma_i = 0.3$  S/m,  $\sigma_e = 1.2$  S/m,  $\sigma_m = 3e-7$  S/m,  $\epsilon_i = 72.3$ ,  $\epsilon_e = 72.3$ ,  $\epsilon_m = 5$ . These values were adapted from computational studies conducting similar investigations [47]–[56]. Since a large range of properties are expected within the population of glial cells [46], different ranges of these parameters were tested to investigate how the dielectric properties of cells influence their response to TTFields (section 2.1.2). The computational studies [20], [44]–[46] were carried out using the Electric Currents Interface of the AC/DC module of Comsol Multiphysics (www.comsol.com). The thin membrane was numerically represented by the contact impedance BC available in Comsol.

In order to apply a homogenous EF the BCs on two opposite sides were chosen as terminals of the voltage type where the others were electrically insulated, representing an ideal parallel plate electrode setup. The default applied voltages of opposite signs were chosen to produce standard field intensity of 1 V/cm, which corresponds to the minimum activity threshold of TTFields intensity. The computational model was validated by comparing numerical results for a spherical cell to the analytical description of the transmembrane voltage of a spherical cell with radius  $r$  (data not shown) [52].

### 2) Results

#### a) Effect of field frequency

The distribution of the EF intensity in and around a cell with standard geometric and dielectric properties (section 2.1.1) is plotted in Fig.1 for selected frequencies (rows) at different stages of mitosis (columns). For a round cell during metaphase the EF distribution inside the cell is uniform with only small perturbations close to the membrane. The intracellular field intensity,  $E_i$  almost equals zero for frequencies <10 kHz (left top in Fig.1, Fig.2). For increasing



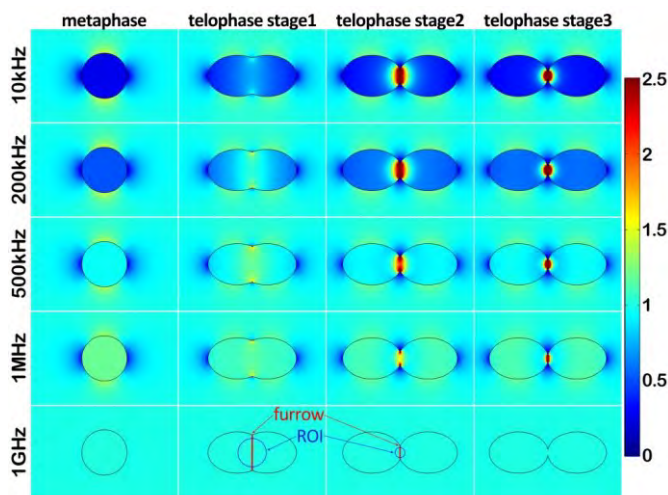


Fig. 1.  $E_i$  distribution in the metaphase cell (column1) and three stages of telophase (columns 2-4) for varying frequency (rows) of the applied EF from left to right with an intensity of 1 V/cm. The color scale is fixed for all panels from 0 - 2.5 V/cm. The bottom panel illustrates the furrow length (red line) and spherical ROI (blue circle) in the telophase cells.

frequency,  $E_i$  gradually increases and finally equals the applied field intensity for frequencies  $>1$  GHz as predicted by Fig.1-2 and discussed in detail elsewhere [45], [46].

During telophase, the low frequency fields do not penetrate the membrane and  $E_i$  is close to zero (column 2 in Fig.1, Fig.2). However, as frequencies increase into the kHz range, a non-uniform field develops within the cytosol with higher field intensities found close to the furrow between the dividing cells (columns 2-4 in Fig.1). The most pronounced and spatially confined EF at the furrow is found for a stage3 cell (column 4 in Fig.1). As the frequency of the field increases, the non-uniformity close to the furrow decreases and the field intensity throughout the cell increases. Thus,  $E_i$  peaks between 100-500 kHz during telophase, with lower peak frequencies observed for later stages of cell division (Fig.2).

For this review article, we evaluated the maximum of  $E_i$  in a spherical region of interest (ROI – blue circles in bottom panel of Fig.1) located at the center of each cell, with a diameter that corresponds to 80% of the furrow length (Fig.2). The figure shows that the maximum value of  $E_i$  increases as the cell

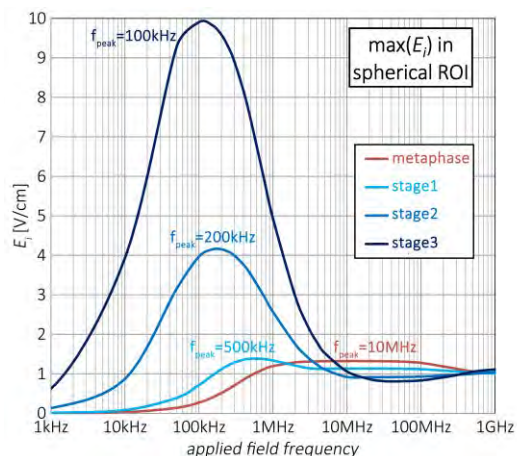


Fig. 2. Maximum  $E_i$  as a function of frequency for 4 different cell cycle stages. The values are measured in central ROIs with a radius of 80% of the furrow length.

progresses through cell division and that its value can exceed the external field strength of 1 V/cm. Secondly, the frequency for which the maximum  $E_i$  occurs decreases as cell division progresses (Fig.2). As a result of the field inhomogeneity inside the dividing cell, the gradient of the EF becomes non-zero. Hence the DEP force component defined as  $\nabla|E_i|^2$  [57], [58] also takes on non-zero values, increasing to maximal values during later stages of telophase with highest values for stage3.

#### b) Effect of cell size

Subsequently, we investigated how the geometric and dielectric properties of the cell influence the EF distribution. Figure 3 shows the maximum of  $E_i$  as a function of frequency for cell radii  $r=\{4,10,15,20\mu\text{m}\}$ . During metaphase the biggest cell with  $r=20\mu\text{m}$  has the highest  $E_i$  for all field frequencies, (Fig.3A), and the peak frequency at which the highest  $E_i$  is found in a cell (10 MHz) is unaffected by cell radius. During telophase the biggest cell has the highest  $E_i$  only for low

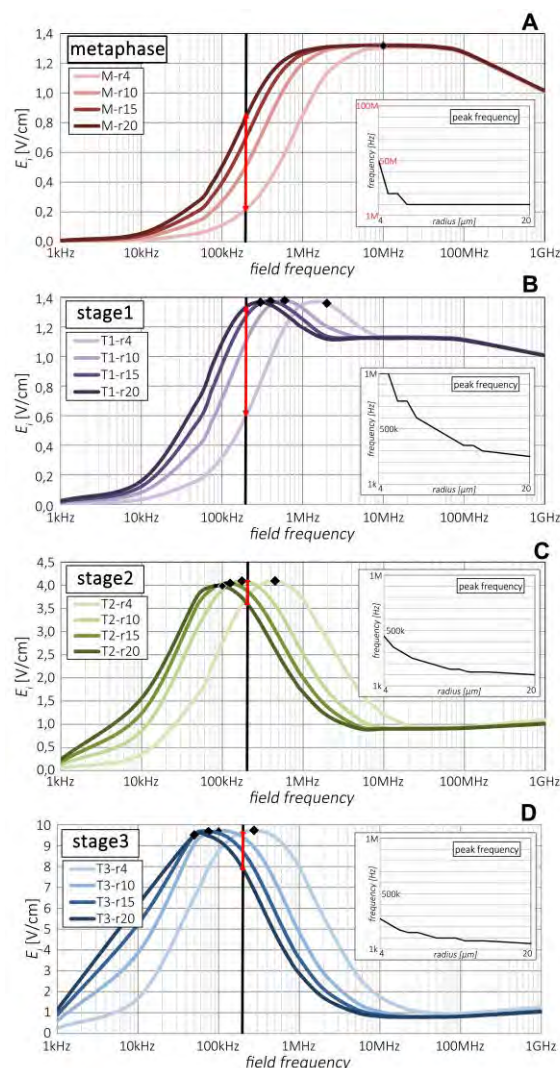


Fig. 3. Maximum  $E_i$  as a function of frequency for 4 selected cell sizes (A) during metaphase and different stages of telophase (B-D). The insets in (B-D) plot the peak frequency as a function of cell radius, corresponding peaks of the 4 selected cells are marked as black diamonds on the curves. The vertical line marks 200 kHz and the span of values is emphasized in red.



frequencies (Fig.3B-D). As the cell radius increases, maximum values of  $E_i$  occur at lower frequencies (insets of Fig.3B-3D). When a constant field frequency of 200 kHz is applied, cell size influences the field exposure inside the cell (vertical lines in Fig.3). During metaphase and stage1 (Fig.3A-B), the highest  $E_i$  is found in the biggest cell and the lowest  $E_i$  in the smallest cell, whereas for stage2 and stage3 the maximum  $E_i$  is found in cells of smaller size (Fig.3C-D).

It is interesting to note that the differences in the maximal values of  $E_i$  obtained at different cell sizes are smaller than 3%, as shown by the similar height of curves in Fig.3 and the dotted lines in Fig.4. This might suggest that the effect of TTFields can be maintained if the frequency is tuned to match the cell size. However, the simulations show that the magnitude of the DEP force component  $|\nabla|E_i|^2|$  is inversely proportional to cell size, likely leading to less effective exposure for bigger cells (solid lines in Fig.4).

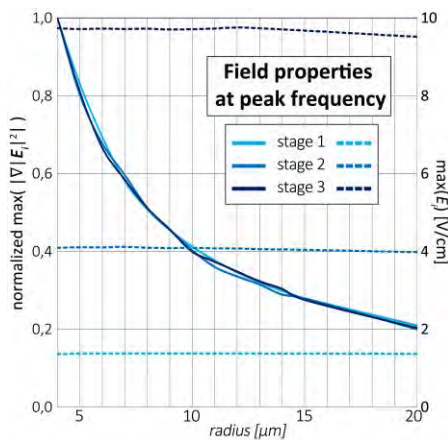


Fig. 4. For each tested cell radius ( $r=4\text{--}20\mu\text{m}$ ), the normalized maximum of  $|\nabla|E_i|^2|$  is plotted as solid lines (left primary axis) and the maximum of  $E_i$  as dotted lines (right secondary axis). Values measured in central ROIs.

#### c) Effect of cell's dielectric properties

Previous computational studies predicted that the dielectric properties,  $\sigma$  and  $\epsilon$ , of the cell are important determinants of the values of  $E_i$  and  $|\nabla|E_i|^2|$ . The most influential parameters were found to be  $\sigma_i$ ,  $\sigma_m$ , and  $\epsilon_m$ , details can be found in [45], [46]. For all parameter variations, peak frequencies varied between 125 kHz-1 MHz for stage1, 50 kHz-400 kHz for stage2, and 50 kHz-250 kHz for stage3. Another consequence of changing the cells dielectric parameters is that for a fixed field frequency of 200 kHz, induced values of  $E_i$  and  $|\nabla|E_i|^2|$  might differ significantly.

Apart from the cell's intrinsic geometric and dielectric properties, the intensity and direction of the externally applied EF influence the EF distribution inside and around the cell. The induced values of  $E_i$  increase proportionally with increasing field intensity and the DEP force component exhibits a quadratic growth [44].

#### d) Effect of cell orientation

The connection between the orientations of dividing cells relative to the field has also been investigated. The field's orientation to the spherical metaphase cell does not change  $E_i$ . The intracellular field remains uniform with parallel EF lines perpendicular to the applied field. But when the cell shape becomes irregular during telophase, the angle between the division axis of the cell and the applied field has significant impact on the intracellular field distribution. The higher the angle between the furrow and the field, the lower the induced maximum  $E_i$  within the cell. This is true for frequencies below 1 MHz, after which the behavior is reversed (results not shown). As example Fig.5, plots the field distribution at 200 kHz for the 3 stages (columns) and 5 different angles from  $0^\circ$  to  $90^\circ$  (rows). The decreasing maximum values within the spherical ROIs (white circle in Fig.5) are printed in the panels. Furthermore, the average EF within the whole cells also decreases (black values in Fig.5). In each column the  $E_i$  in the highly exposed furrow region diminishes as the angle between division axis and field increases from top to bottom.

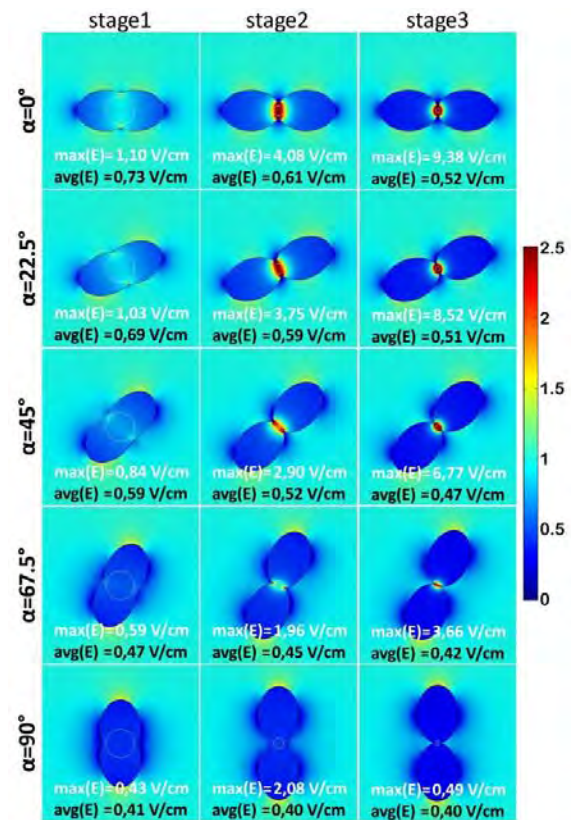


Fig. 5.  $E_i$  distribution induced in a cell during 3 stages of telophase (columns) for varying angle between the division axis and the EF (rows). The field has a frequency of 200 kHz, an intensity of 1 V/cm, and it is applied from left to right. The maximum  $E_i$  in a spherical ROI (white circle) is presented in each panel in white, and the corresponding average  $E_i$  in the whole cell in black.

#### e) Discussion and Future Directions

The ultimate goal of the computational models presented above is to provide insight into the biophysical mechanisms that govern TTFields, starting with the examination of the connection between the intracellular field distribution and the



field parameters (mentioned in section 1.2) that influence treatment efficacy.

**Field frequency:** Experimental results predict that the efficacy of TTFields is frequency dependent and each cell line has a specific frequency for which the inhibitory effect is highest [5]. Additional *in vitro* experiments predict that the optimal frequency for inhibitory effect of TTFields is inversely related to cell size [5], [6]. The computational models confirm that during cell division, the EF intensity peaks in the range between 100-500 kHz with a lower peak frequency for later stages of telophase (Fig.2). It should be noted that the target cells are all in different stages of mitosis in a patient, and therefore there is probably no single frequency that is optimal for all of the cells. However, even if one were to be able to synchronize the target cells to be in stage3 for instance, it might not increase the therapeutic effect of TTFields delivered at a single frequency because of potentially other yet undiscovered biological processes.

The computational models further predict that the cell's geometric (Fig.3) and dielectric properties influence the reported peak frequencies. Because different cell lines have different properties, the simulation results might explain the cell-line specific optimal frequency. It would be insightful to evaluate and measure the size and dielectric properties of different cell lines [59] and compare them to the computational results. The modeling results show that with increasing cell size the peak frequencies decrease (insets Fig.3B-D). The corresponding maximum values of  $|\nabla|E_i|^2|$  also decreases with cell size. It is worth noting that experiments showed that cell volume increases in almost all cell lines treated with TTFields [60]. Thus, increasing cell size during TTFields treatment might be an escape mechanism of the cancer cells, because the intracellular field and DEP component decrease as cell size changes.

**Field Intensity:** TTFields' effect increases with intensity [5], and higher field intensities yield smaller cell counts. The computational modeling confirms that increasing the field's intensity also increases the induced intracellular field and DEP component [44]–[46].

**Direction of division:** In line with experimental results, the computational model predicts decreased intracellular field strengths for cells that are not dividing parallel to the applied field.

When evaluating these results it is important to keep in mind that the models represent single isolated cells with a homogeneous cytoplasm. Yet, within tissue, cells are generally packed, which could cause local inhomogeneity in the extracellular fields, and could to some extent attenuate field distributions. However, the degree to which TTFields penetrate the cells is determined by the properties of the single cell. Thus, it is unlikely that the observation that the intracellular field and DEP depend on the frequency, intensity and direction of the applied field will change when considering models of packed cells. Additionally, the cytoplasm is heterogeneous and contains multiple organelles which would increase the non-uniformity of intracellular

fields. This could possibly lead to local field gradients and DEP forces even when the cell is rounded during metaphase. Thus cytoplasmic heterogeneity is expected to magnify the effects of TTFields.

Let's now turn our attention to how the intracellular EF might disrupt mitosis. Endogenous EFs are believed to play a key role during mitosis [61], [62] as supported by experimental evidence for peak electromagnetic activity during mitosis [63], [64] as well as by physical modeling of the electrostatic forces generated by MTs which are at work during mitosis and influence chromosomal motion [65]–[67]. Thus, it is not unlikely that external electric fields, such as TTFields could disrupt mitosis. It has been speculated that when dividing cells are exposed to TTFields, the tubulin dimers align with the field rather than with the growing MT axis. However, Tuszyński et al. [20] calculated that the interaction energy of a tubulin dimer with an EF of 1 V/cm is too small to affect the dynamics of the dimer. They also proposed that a 1 V/cm EF would be insufficient to exert a major influence on MTs and the cytoskeleton due to Debye screening. Furthermore, they showed that the torque an MT experiences in a 1 V/cm field is 3 orders of magnitude too low to lead to significant rotation. However, the authors did show that the field non-uniformity in dividing cells could cause substantial DEP forces on tubulin dimers and MTs potentially large enough to disrupt cell division. In addition, they showed that under the influence of TTFields significant ionic currents could develop along MTs that might disrupt cellular function. In the future it would be useful to create complex cellular models by combining the computational models presented here with electromechanical models of mitotic spindle dynamics [68], [69]. These models have already been adapted to address possible mechanisms of the effects of ultra-short electrical and mechanical pulses on dividing cells [70]. It would also be useful to measure the magnitude of TTFields within the cells. This task is challenging. However, a promising technique that can measure local EF in cell cultures has been reported [71]. In the future similar techniques might be applicable to experimentally measure the magnitude of TTFields within cells.

## B. Realistic human head modeling

### 1) Materials & Methods

The creation of realistic human head models is a challenging task, which relies on the segmentation of MRI datasets. Typically, the healthy human head will be divided into tissue types of distinct dielectric properties: the scalp, the skull, the cerebrospinal fluid (CSF), the gray matter (GM) and the white matter (WM). The CSF filled ventricles in the center of the head will also usually be identified. There are many different software packages available to achieve this task in a semi-automated manner.

#### a) Head model creation

The first model created for TTFields simulation studies [72], [73] originated from T1 and proton density weighted MRIs (<http://brainweb.bic.mni.mcgill.ca/brainweb>) of the



Colin27 dataset. The freely available Brainsuite software was used for segmentation [74]. The second model used a dataset of a young healthy female consisting of T1, T2, and diffusion MRI (dMRI) datasets [75]. The open-source package SimNibs v1 [76] which uses Freesurfer [77] for segmenting the cortical tissues and FSL [78] for segmenting the outer tissue layers was adapted for this purpose. Brainsuite was used to create the scalp and skull segmentation of the second model. A recent study [79] has employed a similar approach using the almi5 dataset and the SimNibs v2 software (www.simnibs.org). These models relied on datasets of healthy persons, thus the presence of a tumor was modeled by incorporating virtual lesions consisting of two concentric spheres; the inner sphere represented necrosis surrounded by an enhancing tumor [73], [75], [79]. In Korshoej et al. (2017), 24 tumors were systematically introduced at different positions relative to the active transducer-arrays [79]. In Wenger et al, 2016, three more tumor locations were tested, and also more complex shaped, bigger, more realistic dimensions were assumed [39].

The first model of a patient with recurrent GBM treated with TTFields therapy was created by segmenting structural images with ScanIP, a commercial software [80], [81]. More recently, head models of a patient with GBM and a patient with anaplastic astrocytoma were created using T1, T2 and dMRI datasets [82] (Fig.6). To create these models T1 and T2 data were initially processed using the *mri2mesh* algorithm in SimNibs v2 (www.simnibs.org) to produce a preliminary volume mesh. Subsequently, the surface mesh structures and binary tissue masks produced by the algorithm were edited manually using custom code based on meshfix [83], FSL and Freesurfer algorithms. This was done in order to accurately reproduce the patient's anatomy, particularly in the tumor region and its immediate surroundings.

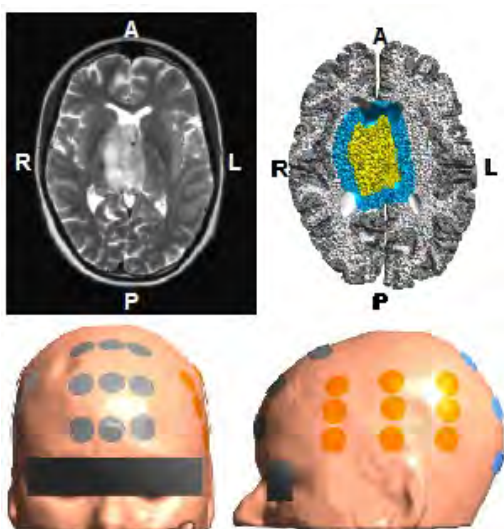


Fig. 6. Example of patient specific head model based on MRI data. The figure shows an axial T2 MRI image (left) obtained from a 23 year-old female patient with deeply seated anaplastic astrocytoma. The three rightmost panels show the head model and tissue segmentation, which was created from the MRI data (T1 and T2) from the same patient. Electrode positioning is evident from the surface reconstruction and electrodes are paired orange/white (LR) and gray/blue (AP).

Following segmentation, the transducer arrays have to be modeled. The studies by Wenger et al. used the 3-matic package of the Mimics v.14 software (www.materialise.com) for this task. The transducers were modeled as 1 mm high cylinders with a radius of 9 mm and the gel layer was represented by cylinders (0.5-2 mm height) of 10 mm radius. For head models created by Korshoej et al. this step was performed automatically with a custom-written Matlab code (www.mathworks.com). In order to complete the model for FE calculation, the final volume mesh has to be created. For models of Wenger et al., this step was performed with Mimics, while open-source tools in SimNibs, Gmsh [84] and meshfix [83] were employed for the patient models.

#### b) Finite element calculation of the electric field distribution

In order to solve the Laplace equation, the virtual tumor studies used the *Electric Currents* physics of the AC/DC package of Comsol (www.comsol.com). Because of the complexity of the model, the solver had to be chosen carefully to obtain convergence (GMRES with SOR preconditioner). For models by Korshoej et al, FE calculations were performed with SimNibs using GetDP with an implemented Galerkin method [85] and residuals for the conjugate gradient solver required to be  $<10^{-9}$ .

To simulate delivery of TTFields to the models, suitable BCs have to be applied. Typically, continuity of the normal component of the current density at all interior boundaries and electric insulation at the external boundaries are considered. In both the virtual tumor models and the patient based models, the external bases of the active transducer arrays were assigned floating potential BCs that set the potential at that boundary so that the integral of the normal component of the current density was 900 mA per transducer array, summing up to 1800 mA peak-to-peak for an active pair of transducer arrays.

To complete the model, the dielectric properties of the different tissue types have to be defined. Isotropic values of electrical conductivity and relative permittivity of different tissue types are listed in the corresponding articles [73], [75], [82]. Studies of related techniques showed that incorporating the anisotropic nature of electric conductivity within the WM significantly affects results [86]–[89]. This anisotropy can be captured by processing diffusion tensor imaging (DTI) data which estimates the diffusion tensor for each voxel, [90], [91]. For the second virtual tumor model, the raw DTI images were corrected and registered with the FSL diffusion toolbox [92] in order to calculate the principal directions (eigenvectors), principal diffusivities (eigenvalues), and the fractional anisotropy. There exist several ways for the subsequent estimation of the conductivity tensor, as described in detail elsewhere [93].

In models by Wenger et al., the direct mapping (dM) method that assumes a linear relationship between the eigenvalues of the diffusion and conductivity tensors was applied [94], i.e.  $\sigma_v = s \cdot d_v$ , where  $\sigma_v$  and  $d_v$  are the  $v$ -th eigenvalues of the conductivity and the diffusion tensors



respectively. Instead of the initially proposed empirical scaling factor  $s$  [94] which is not generally valid, an adapted  $s$  was considered [95]. Additionally, an adapted volume normalized (vN) mapping method was used, which locally matches the geometric mean of the conductivity tensor's eigenvalues in each voxel to the corresponding isotropic conductivity value (either WM or GM) [96]. In order to incorporate tissue anisotropy into the computational models, the conductivity tensor of each voxel was imported into Comsol for FE computation.

For the patient head models, dMRI processing and conductivity estimation with the DM approach was performed using the *dwi2cond* algorithm in SimNibs. The scaling factor was obtained by fitting only the non-pathological regions of the GM and WM tissues of the contralateral hemisphere to standardized values, because the technique remains to be firmly validated for tumor tissue. Values in the tumor tissue were obtained by extrapolation using the obtained fit. Figure 7A shows a conductivity map obtained from dMRI data from a patient with left frontoparietal GBM alongside the corresponding probability density functions (Fig.7C) of the conductivity values. The mean conductivity value in the tumor region was 0.245 S/m and the interquartile range was 0.077 S/m. Thus the estimated conductivity of the tumor was in the same range as previously reported for gliomas *in vivo* [97]–[99] and agreed well with the conductivity values used in the virtual tumor models. Figure 7 also demonstrates the considerable anisotropy (high fractional anisotropy) in the WM tissue, which has been shown to impact the distribution of the estimated field considerably [75]. It is also evident that

the tumor region is characterized by considerable topographical variability in both conductivity and fractional anisotropy, which highlights the importance of individualized head modeling and conductivity estimation. After conductivity estimation, the resulting anisotropic conductivity tensors were imported directly into SimNibs for FE calculations.

For the virtual models by Korshoej et al., a similar approach was adopted to produce a conductivity tensor for WM and GM using *dwi2cond* algorithm. Isotropic conductivities similar to Wenger et al. were used for the remaining tissues, including the tumor and necrosis.

## 2) Results

The simulation-based studies show that TTFields distribution within the brain is heterogeneous [72], [73], [79], [100] and influenced by the complex tissue interfaces, and especially the differences in dielectric properties of the different tissues. The highest field intensities are found in the scalp and skull close to the active transducer arrays. Although the field in the brain tissue on average decreases with increasing distance from the transducers, field strengths are not necessarily higher for tumors close to the active arrays. This is mainly due to shunting of current through surrounding less resistive CSF pathways during LR array activation [79]. Deeper regions with higher field intensities (hot spots) were also observed (Fig.8), caused by the fact that at a tissue interface the field increases in the lower conductivity medium and decreases in the tissue with higher conductivity. This behavior has also been reported in other non-invasive brain stimulation techniques [101]. In addition, the CSF creates low-resistance pathways causing currents to flow through the sulci, ventricles and resection cavities towards deeper regions, which in turn creates local field “hot spots” in deeply seated tumors embedded in WM, as well as in tumors located close to the sulcal fundi and near resection borders [79]. Higher EF intensities were found for the LR array and the field distribution appears to be more uniform in the AP setting. Nonetheless, the average EF intensities in the brain was estimated to be very similar in the two settings,  $|E_{brain}^{LR}| = 1.18$

V/cm and  $|E_{brain}^{AP}| = 1.14$  V/cm [75]. The AP array configuration delivered higher field intensities to superficial tumors, while the LR configuration delivered higher intensities to deeper tumors [79].

Within the tumor, low field values were found in the necrotic core and higher values with a non-uniform distribution were found in the tumor and peritumoral border zone [73], [79]. Again the directional effects, explained above, were responsible for hotspots created in the tumor, which were far more pronounced in the LR setting for the first tumor location tested [75]. The average EF intensities in the enhancing tumor part depended significantly on the tumor location and ranged between  $|E_{shell}^{LR}| \approx 1.20 - 1.65$  V/cm and

$|E_{shell}^{AP}| \approx 0.75 - 1.40$  V/cm [75], [79].

Another aim of the modeling studies was to clarify to what extent the EF distribution depends on assumptions about the

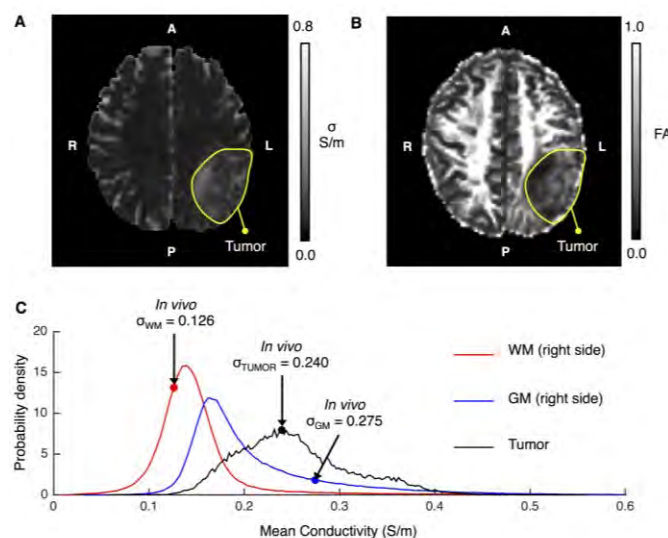


Fig. 7. Conductivity maps and estimation for patient based and virtual tumor models. (A) Axial section of dMRI based conductivity map obtained using SimNibs. The map was created using direct linear mapping based on the right GM and WM tissue and then extrapolating the obtained scale factor to obtain a generalized conductivity map covering the whole brain and tumor. (B) shows the corresponding probability density functions of the conductivity estimates and (C) the fractional anisotropy distribution of the conductivity tensors. As evident from the figures, both distributions in (A) and (B) cover a wide range of values with considerable topographical variability, particularly in the tumor region, which illustrates the potential importance of utilizing patient specific estimates. It is also notable, that the conductivity range and mean values correspond well to *in vivo* estimates.



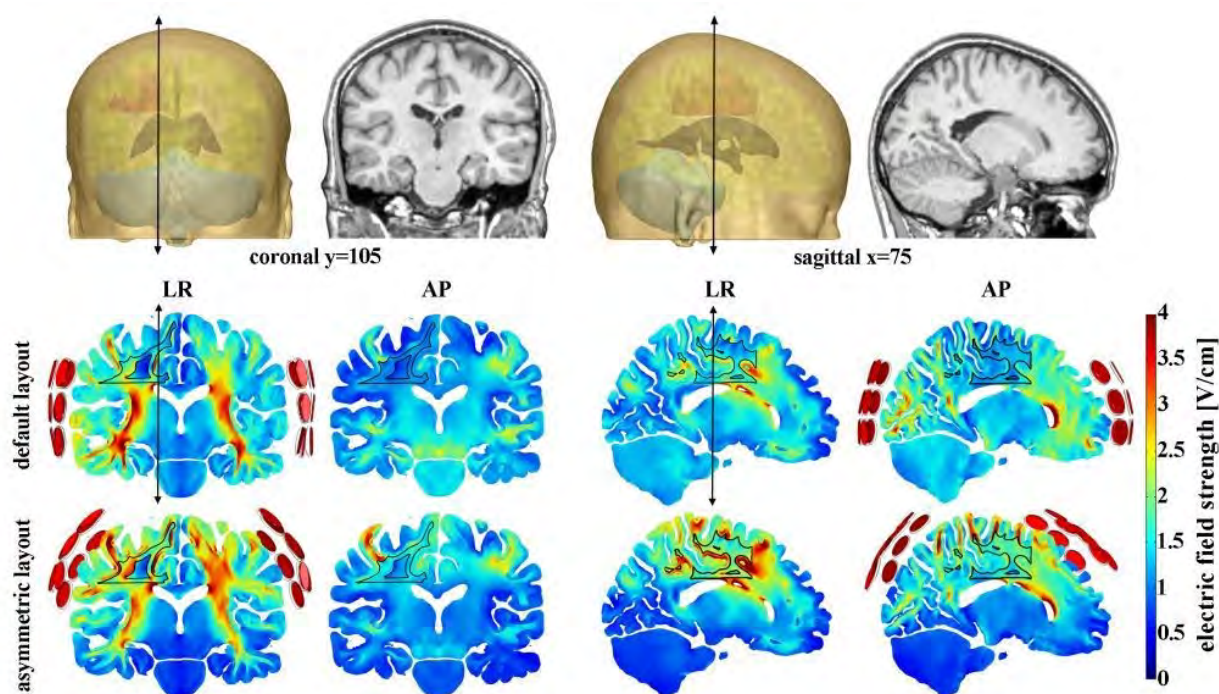


Fig. 8. The distribution of the EF's intensity (V/cm) is presented in two axial slices through a virtual tumor located frontal in the left hemisphere (contour shown in the left hemisphere, anteriorly). Default (2<sup>nd</sup> row) and patient-specific adapted layouts (3<sup>rd</sup> row) are presented for LR and AP setups of the Optune<sup>TM</sup> device. Corresponding anatomical slices and their position in the head model are presented at the top. Reproduced from [38].

dielectric properties of the tissues, and the extent to which tissue anisotropy influences the field distribution [75], [100]. For the second virtual tumor head model, representation of the conductivity tensor using both the dM and the vN methods (section 2.2.1) yielded field distributions that were similar to the field distribution in the isotropic model. The calculated average EF intensities in the brain and tumor showed only minor differences between isotropic and anisotropic models. However, tumor locations in highly anisotropic areas of the WM [79] and possibly also the tumor's intrinsic anisotropy of conductivity can influence the field intensity at the diseased site. Indeed, the field distributions in the patient based models, suggest that the choice of conductivity assignment plays a significant role in determining the field distribution in the regions of pathology. Particularly, the median field intensity is approximately 0.20 V/cm lower in the peritumoral border zone for the patient shown in Fig.7 when the dM anisotropic conductivity tensor is used compared to isotropic scalar conductivity assignment. In WM, GM, and tumor tissue no significant differences in the central tendencies of the field estimates were observed although the choice of conductivity model did affect the topographical distribution of the field in all tissues. Specifically the interquartile range of the paired difference in field estimates for all elements was  $> 0.40$  V/cm for all tissues. The fact that the peritumoral region is more sensitive to the chosen conductivity model, likely indicates that standardized conductivity values for GM and WM do not accurately represent the tissue properties in this region due to the presence of edema and tumor infiltration.

Furthermore, a sensitivity analysis has been carried out to determine how uncertainties in the dielectric properties of

tissues affect the EF in the tumor [75], [100]. Variations of permittivity values by up to 2-fold in all of the head tissues lead to changes in the average field intensity of less than 2% [75]. This is due to the fact, that for TTFields settings the current is mainly resistive as opposed to capacitive, i.e.  $\sigma \gg \omega \epsilon_0 \epsilon_r$  [102]. Furthermore, this result validates the approach of considering a static problem by neglecting the permittivity, as it was done in the patient studies using SimNibs. However, significant differences in the induced EF intensities have been observed when conductivity values of both pathological and healthy tissues are varied by up to 2.5-fold [75]. The percentage difference between the highest and the lowest average field intensity in the brain changes up to 42%. Within the tumor the differences in field intensities can be as large as 68%. The tissues whose conductivity has the greatest effect on the average EF in the tumor are the tumor itself, the skull, and the scalp [75].

The influence of tumor composition on the field intensity was also investigated [79], [100], [103]. The virtual cystic tumors discussed above (with a necrotic core) were replaced with a solid enhancing tumor mass [79], [103]. Although the average field intensity in the active part of the tumor is similar in both cases, the EF distribution is relatively uniform in the solid tumor, but shows hot spots and less exposed areas within the active region, when a necrotic core is introduced.

A consecutive study investigated the influence of tumor size, shape and position on EF intensity [39]. A virtual tumor with the same shape and size as the tumor discussed above was placed at different location within the brain. Two additional tumors with irregular shape and larger sizes were placed in the left hemisphere (Fig.8). The computational



results show that tumor shape and size, up to 26.6 cm<sup>3</sup> total volume, did not have a noticeable impact on the average EF intensity in the tumor, owing primarily to the large size of the individual arrays. Simulations revealed that the induced average EF intensity value remained above 1 V/cm for all tumors irrespective of the direction from which TTFields was delivered. However, visual examination of the field distribution suggested that the default position of the arrays tested in these simulations might not optimal field intensities to all tumors. Tumors in the anterior region are not well covered by the default LR array placed above the ears, although their proximity to the frontal AP patch has been shown to induce high field intensities (Fig.8). For superficial tumors, the patches are too low to induce optimal field delivery. The study therefore investigated how adapting the transducer arrays positions to specific tumor location influenced field intensity. Indeed, for all tumor locations, moving the patches closer to the region containing the tumor increased the induced average EF intensity in the tumor (Fig.8). Details can be found in [39].

Since there exist models of two individuals with the same virtual tumor in terms of size, position, and properties, conclusions about patient variability can be drawn [75], [104]. The second model generally showed higher EF intensities, with average values 20% and 50% higher for LR and AP configurations respectively. The two heads have different shape and size (the first model head is bigger), and an exploratory analysis showed that the median thickness of the scalp and skull are 94% and 75% smaller respectively in the second model. Thickening the skull in the second model and increasing the head size of the second model [39] brings the average EF intensities in the tumor closer to the values observed in the first model. These studies illustrate the large extent to which individual head shape and size, and the geometry and thickness of the tissue compartments [100] influence TTFields distribution within the head.

### 3) Discussion and Future Directions

Currently there are no non-invasive methods to image the induced TTFields in the head during therapy. Only one intracranial measurement of TTFields intensity has been performed on a human subject. This measurement showed that TTFields intensity within the center of the brain ranges between 1–2 V/cm, and is within 10% of the predicted values [6]. The development of realistic human head models has allowed detailed description of EF distribution in the head following Optune treatment. This is an important step towards understanding the basic features of the induced field, which are not entirely intuitive. The induced field is highly non-uniform and depends on the complex tissue interfaces and their dielectric property distributions. This results in regions of high field intensity not only close to active transducers but also in deep areas of the brain.

Realistic computational models have also enabled quantification of the EF intensity delivered to the tumor, and show that TTFields intensity in large regions of tumors exceeds the therapeutic threshold of 1 V/cm, irrespective of

head geometry, tumor location and size, and array configuration. The field estimates are influenced by model uncertainties, particularly by uncertainties of the chosen ohmic tissue conductivities. The conductivity is frequency dependent [105] and the intermediate frequency range is least studied and experimental results often cover the low-frequency or higher frequency regimes. In addition, the values reported in the literature possess a substantial spread. Given that the computational study employing a virtual tumor model demonstrated a clear sensitivity of the calculated fields on the chosen tissue conductivities, specific measurements would be highly desirable and would certainly provide an opportunity to improve the accuracy and precision of the model results. This not only relates to the conductivity of the main tissues (skin, skull, CSF, brain gray and white matter), but also to the conductivity of the tumor tissue, which might possess a wide inter-individual spread due to differences in tumor type and “stage of development”. The latter notion is supported by the documented inter-individual variation in apparent diffusion coefficient (ADC) in the tumor region and also the established correlation between ADC values and glioma grade [106].

Virtual tumor models have the advantage of being versatile and able to simulate virtually every situation in terms of tumor location, shape and size, as well as head shape and size. The influence of each of these parameters can be studied systematically. One study investigated adapting transducer arrays to specific tumor locations, to clarify how beneficial the treatment planning with NovoTAL™ might be. The modeling results confirmed that the EF intensities can be significantly increased when a patient-specific array layout is used. However, only one subject was tested with virtual tumors and another study already predicted differences in the induced field for two different persons. Computational modeling has the potential to identify the properties of the head that result in these differences. One small study started to investigate the effect of different head size and thicknesses of outer tissue layers. It would be possible to deform the virtual tumor model into different shapes and scale tissue to produce a more individual model [107]. However, these techniques might underestimate altered anatomy due to disease (edema, midline shifts, etc.) in a real patient.

Thus, patient head models, which are created by directly segmenting patient MRI datasets, are a highly important addition to the computational simulation of TTFields application in clinical settings. Such patient specific models have recently been applied in a study aiming to investigate the potential benefit of combining TTFields with surgical craniectomy [82]. A clinical phase I trial testing the safety and feasibility of this procedure was recently launched (NCT02893137). This example highlights how computational modeling can facilitate translational research.

Despite the considerable potential of patient specific models, further investigations are required to firmly validate the technique. An important aspect will be the further validation of the dMRI approach for conductivity estimation on a larger number of patients, potentially by correlating



dMRI estimates of conductivity to stereotactic *in vivo* measurements from the same patient [82].

Furthermore, ongoing studies by the authors aim to characterize the importance of tumor locations and morphological characteristics such as size, shape, mean conductivity distribution and fractional conductivity anisotropy on the distribution of the induced field [82]. Such an investigation would be an important addition to the studies performed with the virtual head models, because of the valuable insight on the tumor's heterogeneous environment and its influence on the induced field. A recent study presented a first attempt to create simpler head models that can provide accurate results for calculating the EF distribution for the application of TTFields [108]. However, future feasibility studies based on a number of datasets should address the performance of this simplified model.

Currently, the frameworks available for creating patient-specific models are cumbersome and time-consuming [82]. This is primarily because algorithms for automatic tumor segmentation are inaccurate. Hence considerable manual intervention is required to obtain models that accurately represent patients. For successful clinical implementation of future modeling technologies the time required to create models and run simulation should be minimized. Thus, an effort should be made to improve segmentation and model creation algorithms to obtain the goal of rapid patient-specific modelling; a parallel investigation into how much complexity is needed in a model to produce reliable predictions of the EF distribution should also be performed.

Clinical investigations have shown a favorable safety profile of TTFields and Optune in particular. Already the virtual head models were used to evaluate SAR values in the scalp, skull and brain tissues [73], [75]. In the patient head models, peak SAR values were increased by craniectomy but still within the range of median SAR values previously reported [82]. It was concluded that the treatment would not impose additional risk of overheating or damage of healthy tissue [82]. Apart from investigating induced SAR values, these modeling studies could also be adapted to specifically study the heat distribution in the head from Optune treatment.

There are many avenues through which computational head models could be used to address clinical questions. The tools described here could be employed to conduct a retrospective outcome analysis in which patient-specific models are created and the connection between disease progression and field distribution could be investigated. Computational models combined with a deep understanding on how field distribution influences disease progression could then be used for adaptive treatment planning. Realistic head models of a patient could be created periodically during the course of treatment, reflecting dynamic changes in tumor morphology and tissue properties [82]. These models could be combined with simulations and an understanding of field intensity influences disease progression to optimize TTFields delivery in a dynamic manner throughout the course of treatment.

### III. SUMMARY AND CONCLUSION

In this review, we showed how modelling at different scales can be employed to study TTFields application. At a cellular scale, simulation studies can be used to strengthen physical understanding and basic knowledge of cell-EF interaction. With the creation of realistic human head model it is possible to investigate TTFields in clinical practice by analyzing induced EF distributions in the patient's brain and tumor during Optune<sup>TM</sup> treatment. Important insights can be obtained from these calculations, such as retrospective analysis of treatment outcome as well as prospective personalized treatment planning. In conclusion, TTFields is yet another application, where computational modeling acts as an integral part for further development and efficacy improvement of a therapy. Clinical and engineering communities will greatly benefit by collaborating and drawing from common resources and knowledge.

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# Understanding and Treating Glioblastoma



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## KEYWORDS

• Glioblastoma • MGMT • Repositioning of drugs • Precision medicine • Biomarker  
• Radiomics • Treatment resistance • Immunotherapy

## KEY POINTS

- Molecular biomarkers are entering diagnostics in neurooncology; current efforts aim at developing biomarkers-based treatment concepts.
- Understanding and overcoming resistance at multiple levels is the key challenge in glioblastoma; reviewing the failure of past concept-driven approaches such as antiangiogenic therapies or trials of unselected populations is necessary.
- The failure of recent immunotherapy trials should provide lessons for future development.
- Despite limited options to molecularly stratify glioblastoma into different age groups, patient functional status and age are key factors to consider for treatment decisions.

## INTRODUCTION

The natural disease course in glioblastoma (GB) is invariably grim. A clinical event (eg, a seizure) or a cerebral image incidentally triggers clinical workup, commonly resulting in a maximal safe surgery. Diagnosis is made by careful neuropathological assessment of the tissue, including immunohistochemistry and selected molecular tests. Adjuvant treatments include radiotherapy (RT) to an area of the brain defined by the contrast-enhancing volume plus a safety margin, as well as alkylating chemotherapy with temozolomide (TMZ).<sup>1</sup> Variation at this stage is limited and may include modification of RT (and sometimes chemotherapy) according to age,<sup>2</sup> and the intensification or omission of alkylating chemotherapy according to the methylation status of the promoter region of the *O<sup>6</sup>-methylguanine DNA-methyltransferase* (MGMT) gene<sup>1,3,4</sup> and

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potentially point mutations in the promoter of the *telomerase reverse transcriptase* (*TERT*) gene, resulting in increased telomerase expression.<sup>5</sup>

Currently available GB treatments are not curative but there are subgroups of patients who derive greater benefit from current treatments, radiation, and alkylating chemotherapy, as well as experimental targeted or immune therapies. Features hampering treatment efficacy across many cancers are prominently present in GB: rapid and infiltrative growth, most likely imitating features of normal brain development<sup>6</sup>; clonal heterogeneity with a component of primitive (or stem-like) features, varying over time with treatment selection<sup>7</sup>; and pathologic angiogenesis, resulting in a hypoxic and immunosuppressive microenvironment.<sup>8</sup>

Whereas the concept of molecular subclassification defined by gene expression and DNA methylation has been spearheaded<sup>9</sup> and further refined<sup>10,11</sup> in GB, the immediate clinical impact on the diagnostic classification,<sup>12</sup> treatment, or even trial development has remained limited. Consequently, trials to date do not use epigenetic or genetic criteria to biologically subdivide GB. *MGMT* promoter hypermethylation (despite its relevance as a predictive marker for response to alkylating chemotherapy) has almost no impact on clinical decision-making, except perhaps in elderly patients.

Understanding of molecular characteristics and cell intrinsic mechanisms of GB pathogenesis has evolved in the last decade.<sup>6,9–11,13</sup> The updated 2016 World Health Organization classification of central nervous system tumors<sup>12</sup> integrates genotypic and phenotypic parameters to GB diagnostics, notably the presence or absence of *isocitrate dehydrogenase* (*IDH*) mutations. These and other mutated drivers in GB are putative targets for treatment. Recent studies in colon cancer revealed that subjects with mismatch repair deficiency (dMMR) respond better to anti-programmed death (PD)-1 therapy.<sup>14</sup> Additional studies indicate that other solid tumors with MMR deficiency, including GB, are sensitive to anti-PD1 therapy.<sup>15,16</sup> There is increasing effort to integrate molecularly informed diagnoses into therapy decision-making.<sup>17–19</sup> Although precision medicine in cancer proposes that genomic characterization of tumors can inform personalized targeted therapies, this proposition is complicated in GB by spatial and temporal heterogeneity.<sup>20</sup>

In parallel with the generation of increasingly complex molecular models for ex vivo data analysis, advanced MRI and data analysis (eg, radiomics) are being developed to decipher information about tumors noninvasively.<sup>21</sup>

Despite all efforts and successes in other solid tumors and the enormous power of basic science in neurooncology, a lack of stringent integration of the existing knowledge into clinical (research) practices has left GB lagging behind the current evolution of modern oncology. The focus to date on traditional all-comers trials, as well as the dearth of widely accepted molecular tests and subsequent enrichment strategies, are important obstacles. An example of concepts in which selection might have made a difference includes the antiangiogenic studies with bevacizumab. Despite the post hoc development of a predictive RNA expression signature favoring bevacizumab treatment in proneural subtypes,<sup>22</sup> the proof-of-concept study has still not been planned. Other examples of putative biomarkers that can be used for subject selection include methylation levels for CpG2 in the region of the *CD95 ligand* (*CD95L*) gene promoter as a predictive biomarker for the CD95L inhibitory recombinant protein asunercept combined with reirradiation in recurrent GB<sup>23</sup> and mechanistic target of rapamycin (mTOR) Ser2448 phosphorylation as a predictive biomarker for the mTOR inhibitor temsirolimus in newly diagnosed GB.<sup>24</sup>

In GB, which harms patients by locally destructive brain growth as opposed to systemic metastases, immunosuppression has been extensively studied. Multiple pathways are proposed to mediate GB-associated immunosuppression.



Among these are transforming growth factor beta (TGF- $\beta$ ) and CD95 signaling; checkpoint receptors, such as cytotoxic T cell antigen-4 and PD-1; and intracellular signaling involving tryptophan metabolism and enzymes, such as indoleamine-2,3-dioxygenase (IDO) or tryptophan-2,3-dioxygenase (TDO).<sup>25,26</sup> Although trials to inhibit TGF- $\beta$  have largely failed to date,<sup>27</sup> the success story of checkpoint inhibition in melanoma and other cancers awaits confirmation in GB. Again, current clinical trial data do not support the efficacy of checkpoint inhibitor in all-comers, unselected population trials in GB. However, there is already a path for GB patients harboring microsatellite instability-high (MSI-H) or dMMR to be treated with the PD-1 inhibitor pembrolizumab. The US Food and Drug Administration granted accelerated approval to pembrolizumab for adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumors who have progressed following prior treatment and who have no satisfactory alternative treatment options.

Vaccine-based immunotherapies vary in design with respect to target selection and vaccine generation. Targets selected for vaccine development in GB include monogenic approaches, such as epidermal growth factor receptor variant III (EGFRvIII),<sup>28</sup> IDH1 (R132H),<sup>29,30</sup> or H3.3K27 M<sup>31</sup>; predefined multiepitope approaches, such as in IMA950<sup>32</sup>; profiling-based selection of a limited number of targets (eg, glioma actively personalized vaccine [GAPVAC]); unbiased approaches with undefined tumor-derived peptides (eg, HSPPC-96); or whole tumor cell lysates (eg, DCVax). To date, well-conducted phase 3 randomized controlled trials, such as ACT IV (examining the addition of rindopepimut, a vaccine against epidermal growth factor receptor variant III (EGFRvIII), to standard of care in newly diagnosed EGFRvIII mutant GB) have not demonstrated efficacy for glioma vaccines.<sup>28,33</sup> The failures in these trials should not distract investigators from developing further vaccine trials in glioma subjects. Instead, important questions, such as target and subject selection, vaccine vehicle, and combination strategies should be addressed upfront in any vaccine trial. This will require innovative, well-designed clinical trials, including assessment of posttreatment tumor tissue. Only then can the magnitude and nature of the intratumoral immune response in response to treatment, and the mechanisms of response and resistance in correlation to peripheral immune biomarkers, imaging parameters, and outcome, be understood.

## CURRENT CHALLENGES AND OPPORTUNITIES

Several groups have proposed that GB is a widespread disease of the brain and not a focal malignant growth. The efficacy of currently available therapies is likely limited by GB's propensity for rapid and infiltrative growth. GB cells interconnect via a functional tumor cell network composed of thin and very long membrane tubes called tumor microtubes (TMs),<sup>6</sup> most likely imitating features of brain development. Growth associated protein 43 (Gap43) and tweety-homolog 1 (Tthy1), 2 already known molecular drivers of TM formation in GB, also play an important role in neurodevelopment.<sup>34</sup> Given the prominent role of TMs, discovering and exploring functional candidates to target and disrupt the network will be a challenge but also an opportunity for the future.

### *Improving Standard Therapies*

Maximal safe surgery has shown to be beneficial for subjects in several trials and the extent of surgical resection is often among the most important prognostic factors in trials. Despite the conceptual challenges of further improving a local treatment, surgery is key for tissue sampling from different areas of the tumor, thus allowing spatial annotation of samples to model heterogeneity in GB. Therefore, it seems plausible to



adapt and refine surgical techniques with the addition of fluorescence to dissect GB cell compartments with lower or higher oxygen levels and differential stem cell content,<sup>35</sup> or with intraoperative MRI to optimize macroscopic tumor removal.<sup>36</sup>

RT to a limited part of the brain (despite the conceptual shortcomings of focal treatments) can likewise further improve radiation target definition (ie, using metabolic imaging<sup>37</sup>) and avoid neurotoxicity (eg, with protons by reducing nontarget tissue dose), although the overall clinical benefit of dosimetric advantages in GB patients remains to be determined.<sup>38</sup> Also, the claimed differential DNA repair pathway choice following proton versus photon radiation<sup>39</sup> needs clinical substantiation.

Tumor-treating fields (TTFields) use alternating electrical fields to inhibit mitoses via disruption of the spindle apparatus.<sup>40</sup> In a randomized trial, the addition of TTFields to standard RT and TMZ in newly diagnosed GB extended overall survival (OS) (hazard ratio [HR] 0.64, 99.4% CI 0.42–0.98,  $P = .004$ ).<sup>40</sup> Whether the magnitude of OS benefit justifies the individual burden and the societal cost is yet to be determined. The long-term relevance of these fields will be determined by whether they are routinely integrated into daily practice and the success (or not) of other concepts (see later discussion).

Other recent data regarding improving the standard of care treatment concern the intensity or duration of TMZ. There is no clear benefit to extending TMZ maintenance therapy beyond 6 cycles.<sup>41</sup> In contrast, results from the CeTeG/NOA-09 phase III trial in subjects with newly diagnosed hypermethylated *MGMT* GB suggest an OS benefit for the combination of RT with lomustine (CCNU) and TMZ<sup>4</sup> (see later discussion).

## UPDATE ON THE ELDERLY

According to the Central Brain Tumor Registry of the United States (CBTRUS) statistical report, which comprises data on subjects with malignant primary central nervous system tumors diagnosed between 2006 and 2010, the median age at GB diagnosis is 64 years.<sup>42</sup> This means that almost half of all patients diagnosed in the United States with GB are elderly (age  $\geq 65$ –70 years) as defined in GB clinical trials. Treatment principles should be the same for both elderly and young GB patients, with a focus on maximizing benefit and minimizing risk from every intervention. However, a more detailed assessment of the risks and benefits are needed for elderly patients because the benefit is generally not as great in elderly compared with younger patients. Based on a variety of trials in elderly subjects, options could include standard RT and alkylating chemotherapy as per standard of care in younger patients, hypofractionated RT and TMZ, RT alone (either standard or hypofractionated schemes), or TMZ alone (Table 1).

In patients with good Karnofsky Performance Status (KPS) greater than or equal to 70, aged 65 to 70 years, and with hypermethylated *MGMT* promoter, combined hypofractionated RT and TMZ is recommended based on randomized data from CCTG CE.6/EORTC 26062 (Canadian Clinical Trial Group (CCTG) CE.6/European Organization for Research and Treatment of Cancer (EORTC) 26062).<sup>43</sup> As long as randomized data on TMZ monotherapy (or the previous CETEG regimen) versus chemoradiation are lacking, TMZ alone seems reasonable in *MGMT*-methylated elderly patients when poor KPS or patient preference suggests that combined treatment may be too toxic.

In patients with KPS 70 years and older, and age 65 to 70 years and older, unmethylated *MGMT*, hypofractionated RT and TMZ is also recommended, recognizing that the benefit of adding TMZ is less in the unmethylated *MGMT* population.<sup>43</sup> Similarly, RT alone seems reasonable in unmethylated *MGMT* elderly patients when poor KPS or patient preference suggests that combined treatment may be too toxic. Further research on patients with unmethylated *MGMT* is needed.



**Table 1**  
**Compilation of therapy options and recommendations for patients with glioblastoma in different age groups according to Karnofsky Performance Status<sup>a</sup>**

MGMT	Age (y)	Karnofsky Performance Status	First Choice	Second Choice
Hypermethylated or undetermined	>70	50–70	TMZ	Hypofractionated (Hypo) RT or TMZ
	>70	>70	Hypo RT or TMZ	TMZ
	<70	<70	Hypo RT or TMZ	(TMZ)
	<70	>70	RT or TMZ	—
Unmethylated	>70	50–70	Hypo RT	(Hypo RT or TMZ)
	>70	>70	Hypo RT	Hypo RT or TMZ
	<70	<70	Hypo RT	Hypo RT or TMZ
	<70	>70	RT or trial	RT or (TMZ)

<sup>a</sup> Regimens are depicted as hypofractionated RT-TMZ<sup>43</sup> or RT-TMZ.<sup>68</sup>

## RECENT TRIALS

CCTG CE.6/EORTC 26062 (the aforementioned randomized phase III trial in elderly subjects comparing hypofractionated RT alone or in combination with TMZ) clearly has an impact on practice and provides evidence for shorter chemoradiation schedules for select subjects and advocates for TMZ use in these subjects, although the authors of this review question the utility of testing for *MGMT* in subjects with good KPS because combined chemoradiation is recommended regardless of *MGMT*. In contrast, other recent trials also aimed to change practice but largely failed. Lessons may or may not be gleaned from these negative trials.

ACT IV was a randomized, double-blind, phase III trial, which recruited adult subjects with newly diagnosed GB with centrally assessed EGFRvIII expression from 165 hospitals in 22 countries. Subjects were required to have undergone a maximal surgical resection and completion of standard RT and concurrent TMZ without progression. During TMZ maintenance therapy (6–12 cycles), subjects were randomized the EGFRvIII vaccine rindopepimut (500 µg admixed with 150 µg GM-CSF) or control (100 µg keyhole limpet hemocyanin), administered via monthly intradermal injection until progression or intolerance. The addition of rindopepimut failed to improve OS with a median OS of 20.1 months (95% CI 18.5–22.1) in the rindopepimut group versus 20.0 (95% CI 18.1–21.9) months in the control group resulting to a HR of 1.01 (95% CI 0.79–1.30,  $P = .93$ ).<sup>28</sup> Because ACT IV followed a promising small, uncontrolled trial of rindopepimut, the lessons learned should include an even higher skepticism concerning small, uncontrolled trial data.<sup>33</sup> This earlier trial also demonstrated an absence of EGFRvIII in rindopepimut-treated tumor specimens and was considered a proof of benefit from rindopepimut.<sup>44,45</sup> However, analysis of posttreatment tumor specimens from ACT IV reveal that a variable percentage of subjects lose EGFRvIII (based on RT-PCR) regardless of treatment arm, raising suspicion of the limited relevance of the EGFRvIII mutation in general. Such information could have been detected earlier with a control in the earlier study.<sup>28,46</sup> Interestingly, contrasting data from 106 subjects demonstrated that EGFRvIII status was unchanged at recurrence in 35 of 40 subjects with EGFR-amplified primary tumors (87.5%).<sup>47</sup> Four subjects lost and 1 subject gained EGFRvIII positivity at recurrence.<sup>47</sup> Agreement on methodological discrepancies for defining EGFR amplification and EGFRvIII positivity may solve the issue. Despite this negative phase III trial of EGFRvIII-directed immunotherapy,<sup>28</sup> the target



may still be relevant for precision approaches; for example, with the drug-antibody conjugate composed of the humanized chimeric EGFR-targeted monoclonal antibody ABT-806 conjugated via a stable maleimidocaproyl linker to the tubulin inhibitor, monomethylauristatin.<sup>48</sup>

After the failure of bevacizumab to demonstrate an OS benefit when added to standard of care in the newly diagnosed setting, the Bevacizumab, Lomustine, or Both (BELOB) trial provided a promising survival signal in recurrent GB, which prompted the EORTC 26101 phase II trial to be transformed into a full phase III study. BELOB demonstrated improved OS at 9 and 12 months for combined bevacizumab and lomustine versus either agent alone. Of note, bevacizumab was not accessible in the Netherlands, where the BELOB study was performed, thus restricting crossover to bevacizumab in the control group ( $n = 1$ ).<sup>49</sup> The subsequent randomized, phase III EORTC 26101 compared lomustine with or without bevacizumab. Despite prolonging progression-free survival (PFS) (HR 0.49, 95% CI 0.39–0.61), combined lomustine and bevacizumab treatment does not confer an OS advantage (HR 0.95, 95% CI 0.74–1.21,  $P = .650$ ) compared with treatment with lomustine alone in subjects with progressive GB.<sup>50</sup> In this study, crossover to bevacizumab occurred in 35.5% of subjects in the control arm; whereas 18.7% of subjects in the combination arm continued bevacizumab at progression.

Large-scale clinical trials are currently evaluating the efficacy of immune checkpoint inhibitors, namely nivolumab, in newly diagnosed and recurrent GB. Whereas the trials in newly diagnosed subjects separated according to *MGMT* promoter methylation status are ongoing, results from the study in progressive GB comparing nivolumab and bevacizumab have been reported. This trial randomized 369 subjects at first progression after standard of care to nivolumab 3 mg/kg every 2 weeks ( $n = 184$ ) or bevacizumab 10 mg/kg every 2 weeks ( $n = 185$ ). The most common adverse events leading to discontinuation ( $>2$  subjects in either the nivolumab or bevacizumab arm) were cerebrovascular accident (0% and 2%, respectively) and pulmonary embolism ( $<1\%$  and 2%, respectively). PFS favored bevacizumab (HR = 1.97, 95% CI 1.57–2.48) with median PFS 3.5 months (2.9–4.6) for bevacizumab and 1.5 months (1.5–1.6) for nivolumab. OS was similar in this unselected subject population (HR = 1.04, 95% CI 0.83–1.30,  $P = .76$ ) with median OS 10.0 months (9.0–11.8) for bevacizumab and 9.8 months (8.2–11.8) for nivolumab.<sup>51</sup> CheckMate 498 (nivolumab or TMZ in combination with RT in newly diagnosed subjects with *MGMT*-unmethylated GB) and CheckMate 548 (nivolumab or placebo in combination with RT plus TMZ in newly diagnosed subjects with *MGMT*-methylated or indeterminate GB) are ongoing. These trials also do not enrich for subjects more likely to benefit from the immune intervention.<sup>16</sup>

As previously mentioned, the CETEG trial used *MGMT* promoter hypermethylation to identify subjects most likely to benefit from alkylating chemotherapy. Newly diagnosed GB subjects harboring a hypermethylated *MGMT* promoter were randomized (1:1) to standard chemoradiation with TMZ concurrent and adjuvant for 6 cycles versus experimental therapy with RT and CCNU/TMZ. The experimental chemotherapy was given as 6 42-day courses of CCNU at 100 mg/m<sup>2</sup> on day 1 and TMZ 100 mg/m<sup>2</sup> on days 2 to 6. The first cycle of alkylating chemotherapy was dosed to coincide with days 1 to 6 of RT, replacing continuous concomitant TMZ. The TMZ dose was adapted according to tolerance. The trial randomized 141 subjects (63 TMZ, 66 CCNU/TMZ) with 129 subjects in the modified intention-to-treat (mITT) population of subjects receiving at least 1 dose of study drug. OS was superior in the CCNU/TMZ arm as compared with the TMZ arm ( $P = .049$ ) after stratification for recursive partitioning class and center. In the mITT population, median OS trended toward benefit in the CCNU/TMZ arm at 37.9 months (95% CI 29.2–51.4 months)



compared with 31.4 months (95% CI 27.0–44.8 months) in the TMZ arm (HR 0.60, 95% CI 0.35–1.03,  $P = .064$ ).<sup>4</sup> This trial constitutes an advantage in the group of GB subjects sensitive to alkylating chemotherapy. Due to its limited size, adaption for unevenly distributed risk factors was necessary. Whether a desired confirmatory trial is feasible, given the wide availability of the drugs and the reasonable costs, needs to be discussed.

The sheer number of negative GB trials over the past years despite concepts or compounds that work well in other diseases should trigger appraisal of potential factors contributing to these failures:

- More than in other solid malignancies, residual tumor after surgery may harbor yet unknown properties that limit treatment efficacy. An argument for this is the newly discovered network of TMs.<sup>6</sup>
- There is a failure to conceptually understand that the overarching principle to be tackled is the heterogeneity of the disease<sup>20</sup> and there is a lack of smart, tolerable combination approaches that appropriately tackle this issue.
- Molecular diagnostics, wherever possible, should be used to improve accuracy of patient selection.
- There was failure to decide if standard of care for all GB subjects should include TMZ<sup>1</sup> (and/or TTFIELDS<sup>40</sup>) or if treatment should be better individualized.
- A rush to pivotal, phase III trials driven by the rules of the market and regulatory bodies for approval prevents step-wise understanding, building on controlled early-phase data, as well as prudent use of scientifically sound biomarkers, for determining subsets of patients who benefit.
- Trials at recurrence are largely built on information of the newly diagnosed disease.
- The measures to determine treatment response or resistance are largely MRI-based, which, despite all standardization,<sup>52</sup> may be insufficient compared with liquid biopsies or radiomic integration of data.<sup>21</sup>
- Currently, trials of targeted therapies and immunotherapies in GB are mainly in unselected subject groups.

In the following sections, some of these concepts are discussed.

## PRECISION MEDICINE APPROACHES

Precision neurooncology relies on the existence of biomarkers that predict response and ultimately benefit from a given therapy. The most prominent example for a predictive biomarker in gliomas so far is *MGMT*.<sup>1,3</sup> However, some investigators suggest that predicting response to TMZ is more complex than just *MGMT* methylation status and defining the right subgroups that do not benefit from TMZ may also involve global methylation profiles and *TERT* status.<sup>5</sup>

Examples of putative predictive biomarkers exist. Patients with newly diagnosed GB harboring a proneural subtype based on expression analyses<sup>53</sup> may derive benefit from the addition of VEGF antibody bevacizumab to standard treatment. If independently confirmed, this would make the proneural subtype a predictive lesion for response to bevacizumab.<sup>22</sup> Similarly, lower levels of methylation of the CpG2 in the promoter of the *CD95L* were predictive for an improved OS with the *CD95* inhibitory treatment with asunercept (APG101) in combination with reirradiation compared with reirradiation alone. Interestingly, patients with lower methylation of the promoter treated with reirradiation alone (ie, not treated with the *CD95* inhibitory therapy) did worse.<sup>23</sup> Also, based on retrospective analysis, mTOR Ser2448 phosphorylation is



an interesting putative predictive biomarker for the response to the mTOR inhibitor temsirolimus plus radiation in patients with newly diagnosed GB without *MGMT* promoter methylation.<sup>24</sup> This seems even more important because, without population preselection, mTOR inhibition is not only ineffective but may even confer a survival disadvantage compared with the standard of care. The addition of a different mTOR inhibitor, everolimus, in a recent controlled study did not provide any advantage in an unselected group of subjects with newly diagnosed GB irrespective of *MGMT* status.<sup>54</sup> In some GBs, B-raf proto-oncogene (*BRAF*) mutations may indicate response to *BRAF* inhibitory treatments.<sup>55</sup> Only recently, an association between a reduced capacity of the tumor cells to repair DNA lesions (MMR deficiency) and positive response to immune checkpoint inhibition has been proposed for lung cancer.<sup>14</sup>

Therefore, well-considered allocation of subjects to clinical trials based on the molecular characteristics of the tumor, as well as necessary retrospective validation of potential biomarkers, is essential in a clinical setting. Current concepts prospectively using biomarkers to enrich for potentially benefitting patients are the Individualized Therapy for Relapsed Malignancies in Childhood (INFORM) trial<sup>56</sup> and the Nationale Centrum für Tumorerkrankungen (NCT) Neuro Master Match (N<sup>2</sup>M<sup>2</sup>), a trial of molecularly matched targeted therapies plus RT in subjects with newly diagnosed GB without *MGMT* promoter methylation.<sup>19</sup> The GB Adaptive, Global, Innovative Learning Environment (AGILE) consortium is planning to take a differential approach by reassessing potential biomarkers from an unselected cohort with given therapies first and integrating this information via adaptive processes to enrich while the trial accrues.<sup>57</sup>

Similar concepts are also being developed for the recurrent disease. One example is that subjects with progressive GB undergo resection for extensive biomarker analysis to allow selection of appropriate treatments from a large set of agents.<sup>18</sup> The concept and potential candidate drugs are outlined in [Fig. 1](#).

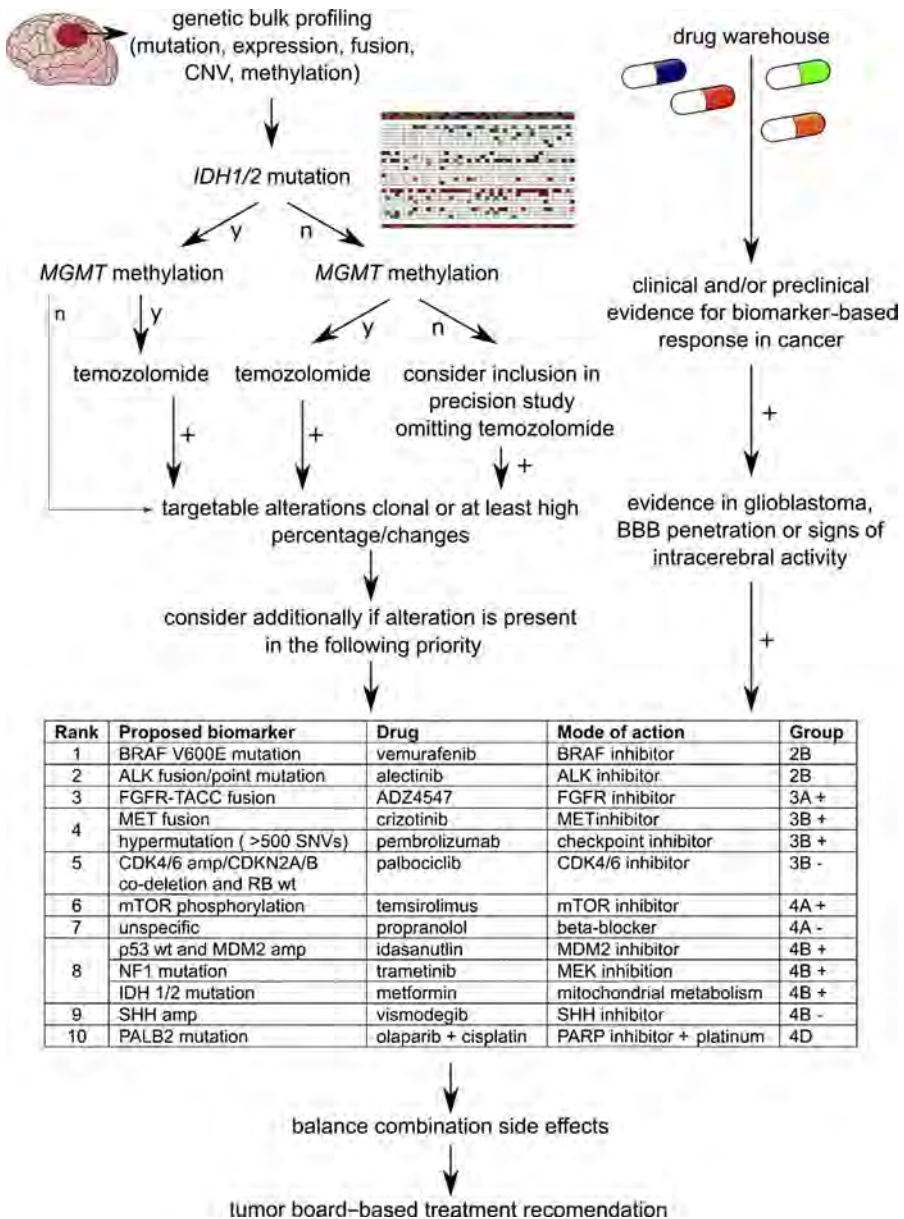
## IMMUNOTHERAPY

Immunotherapy may represent the next big step for patients with GB ([Fig. 2](#)). In addition to the successes in other malignancies, this optimism is fueled by single cases and attractive concepts. Independent of the approach (eg, checkpoint inhibition, targeted vaccine, or adoptive T-cell transfer), the clonal representation of the target antigen and the immunosuppressive microenvironment must be taken into account for clinical development. For instance, EGFRvIII is a subclonal antigen with heterogeneous expression in the tumor tissue, which may, in theory, be subjected to immune evasion. The early founder mutations IDH1R132H<sup>29</sup> and H3.3K27M<sup>31</sup> represent clonal antigens.

Several chimeric antigen receptors (CARs) are in clinical development for GB-targeting tumor antigens, such as interleukin 13 receptor- $\alpha$ 2, EGFRvIII, and human epidermal growth factor receptor 2. A proof-of-concept report in a patient with recurrent, multifocal GB validates a robust antitumor killing capability of CAR T cells in general.<sup>58</sup> In a series of 10 subjects, intravenous delivery of a single dose of autologous T cells redirected to the EGFRvIII mutation by a CAR showed feasibility of manufacturing and intravenous delivery of CAR T-EGFRvIII cells.<sup>59</sup> There was no evidence of a cytokine release syndrome and CAR T-EGFRvIII cells transiently expanded in the peripheral blood.<sup>59</sup>

- Concepts to enhance activity of drugs and prevent development of resistance deserve exploration of strategies against immune inhibitory pathways, potentially





**Fig. 1.** Path toward precision. Paradigmatic work flow from a recurrent GB tissue sample is outlined. ALK, anaplastic lymphoma receptor tyrosine kinase; amp, amplification; BBB, blood-brain barrier; CDK, cyclin-dependent kinase; CDKN 2A/B, cyclin-dependent kinase inhibitor; CNV, copy-number variation; FGFR, fibroblast growth factor receptor; MDM 2, mouse double minute; MEK, mitogen-activated protein kinase; MET, hepatocyte growth factor receptor; n, no; NF1, neurofibromin; PALB 2, partner and localizer of BRCA; poly (ADP-ribose)-polymerase; RB, retinoblastoma; SHH, sonic hedgehog; SNV, small nucleotide variants; TACC, transforming acidic coiled-coil; wt, wild-type; y, yes.







have failed to learn from successes and defeats. Neurosurgical and standard chemoradiation approaches may have reached their boundaries; yet, the most and least benefitting patients, as well as the mechanisms of secondary resistance, are not understood.

Concepts currently explored in radiation oncology focus on target definition and use of alternative radiation qualities. After many years of focusing on targeting angiogenesis,<sup>50,65,66</sup> the field has shifted to immunotherapies, mainly checkpoint inhibition but also targeted (vaccination) approaches. Pathway inhibition has maintained momentum, with the biggest change in the last decade being appropriate preselection of subjects based on the proposed mechanism of action.<sup>67</sup> There is a need for academically driven drug development and design of trials with the focus on understanding the mechanisms of response or resistance rather than striving for short-term approval. Similarly, immunotherapy trials should also focus on getting as much information about response and resistance from each subject to inform subsequent steps (backwards translation) and rapid evolution of concepts to trials.

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# Treatment of glioblastoma in adults

Wolfgang Wick<sup>ID</sup>, Matthias Osswald, Antje Wick and Frank Winkler

**Abstract:** The diagnosis of a glioblastoma is mainly made on the basis of their microscopic appearance with the additional determination of epigenetic as well as mutational analyses as deemed appropriate and taken into account in different centers. How far the recent discovery of tumor networks will stimulate novel treatments is a subject of intensive research. A tissue diagnosis is the mainstay. Regardless of age, patients should undergo a maximal safe resection. Magnetic resonance imaging is the surrogate parameter of choice for follow up. Patients should receive chemoradiotherapy with temozolomide with the radiation schedule adapted to performance status, age and tumor location. The use of temozolomide may be reconsidered according to methylguanine DNA methyltransferase (*MGMT*) promoter methylation status; patients with an active promoter may be subjected to a trial or further molecular work-up in order to potentially replace temozolomide; patients with an inactive (hypermethylated) *MGMT* promoter may be counseled for the co-treatment with the methylating and alkylating compound lomustine in addition to temozolomide. Tumor-treating fields are an additive option independent of the *MGMT* status. Determination of recurrence is still challenging. Patients with clinical or radiographic confirmed progression should be counseled for a second surgical intervention, that is, to reach another macroscopic removal of the tumor bulk or to obtain tissue for an updated molecular analysis. Immune therapeutic approaches may be dependent on tumor types and molecular signatures. In newly diagnosed and recurrent glioblastoma, bevacizumab prolongs progression-free survival without affecting overall survival in an unselected population of glioblastoma patients. Whether or not selection can be made on the basis of molecular or imaging parameters remains to be determined. Some patients may benefit from a second radiotherapy. In our view, the near future will provide support for translating the amazing progress in understanding the molecular background of glioblastoma in to more complex, but promising therapy concepts

**Keywords:** antiangiogenesis, checkpoint inhibitors, high-LET radiotherapy, malignant glioma, precision medicine, tumor membrane tubes, vaccination

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## Background

Glioblastoma is a fatal disease with the majority of patients dying within 15–18 months from diagnosis, with less than 5% of patients alive at 5 years.<sup>1</sup> Even within the more favorable selected clinical trial patient population the 5-year survival rates are around 10%.<sup>2</sup> Age <50 years and a complete macroscopic tumor removal are associated with longer survival; on a molecular level these tumors often exhibit two favorable molecular aberrations: O<sup>6</sup>-methylguanine DNA methyltransferase (*MGMT*) promoter methylation<sup>2,3</sup> or isocitrate dehydrogenase (*IDH*) mutation.<sup>4</sup> There is a large disconnect between enormously

evolving preclinical concepts and a very limited clinical therapeutic armamentarium, which is somewhat resistant to the novel biological concepts, that is, to apply the available biomarkers for treatment decisions, and on the other hand easy to impact by nonconventional strategies, that is, by regionally different one-fits-all approaches with drugs like cannabis, valaciclovir or methadone.

## Epidemiology

The incidence of primary brain tumors between 2007 and 2011 was 21.4 per 100,000 individuals,

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with an incidence of gliomas of 6.6 per 100,000 people of which about half were glioblastomas.<sup>1</sup> For reasons unknown, there is regional variability in the incidence. The rate for glioblastoma in Japan is <50% of that in Scandinavia or the United States. The incidence of glioblastoma in general increases with age, with the most pronounced increase in glioblastoma incidence (per 100,000 people) ranging from 0.15 in children and 0.41 in young adults to 13.1 in those aged 65–75 years and 15.0 in individuals between 75 and 84 years of age.<sup>5</sup>

### Risk factors

Overall, manageable risk factors are hardly known. Specifically, therapeutic radiation in long-term survivors seems to have a dose and volume dependent impact.<sup>6</sup> These doses are not reached with diagnostic doses of radiation, for example, by regular cranial computed tomographies (dose in the range of 1–3 milli Sievert, comparable with the annual environmental radiation exposure or a long-distance flight). Relevance of other factors, like cytomegalie virus infection or mobile phone use has not been confirmed. In addition to the well described familial tumor syndromes, there are genetic associations for example, rs4977756 in the cyclin-dependent kinase inhibitor 2A (*CDKN2A*) and the *CDKN2B* gene,<sup>7,8</sup> a retinoic acid modulator *CCDC26* on 8q24,<sup>9</sup> pleckstrin homology-like domain family B member 1 (*PHLDB1*) on 11q23.3,<sup>10</sup> the TP53 (cellular tumor antigen p53) polyadenylation site rs78378222 on 17p13.1,<sup>11</sup> and rs11979158 and rs2252586 in the epidermal growth factor receptor (*EGFR*) gene on chromosome 7<sup>12</sup> with a higher likelihood of glioblastoma in one family.

Also, telomerase reverse transcriptase (*TERT*) and telomerase RNA component (*TERC*), which are both involved in regulating telomere length, have been suggested as interesting candidate genes for increased glioma risk in genome-wide association studies.<sup>13,14</sup>

Overall, until now, there is no firm manageable risk factor, no screening test or prevention concept available for glioblastoma. In turn, there is not role for regular magnetic resonance imaging (MRI) scans in relatives of glioblastoma patients.

### Biological considerations

Glioblastoma is a whole brain disease with a variable focal increase in proliferation generating a

tumor mass, which then may become symptomatic. These days, more weight is put on the largely invisible, diffusely infiltrating part potentially consisting of a functional network of glioblastoma cells (and other brain cells) connected by transmembrane nanotubes (tumor microtubes or ‘TMs’).<sup>15</sup> In addition to the classical hallmarks, such as pathological angiogenesis, necrosis and the immunologically cold environment,<sup>16</sup> these networks not only provide a more stringent concept for the diffuse infiltrative growth, but may also serve as the long-awaited Achilles’ heel for this disease.

### Basic requirement for diagnosis

The diagnosis of a glioblastoma is made tissue-based according to the most recent update of the World Health Organization (WHO) classification of brain tumors including immunohistochemistry and selected molecular tests.<sup>17</sup> Recently, a high-throughput methylation-based classifier<sup>18</sup> has been shown to effectively diagnose glioblastoma based on quantitative methylation classes.<sup>19</sup>

### Standard of care

#### Surgery

The standard of care for adult patients largely irrespective of age, but with a good performance status with radiographically suspected newly diagnosed glioblastoma is a maximal safe surgical resection. This may result in a stereotactic or open biopsy in some patients with tumors in eloquent areas or in a removal of all contrast-enhancing parts of the disease in adequate patients. The goal of a complete macroscopic resection may be reached with the help of intraoperative imaging<sup>20</sup> or fluorescence-guided visualization of tumor tissue with the aid of 5-aminolevulinic acid.<sup>21,22</sup> As long as the community is not prepared to complete a controlled trial on the relevance of resection at progression, we will base our recommendations for a second surgery on some pragmatism, the need for an updated molecular or tissue diagnosis in cases with molecular-directed treatment options, the need for reduction of global or focal intracranial pressure, local expertise and patient preference.

#### Radiotherapy

Radiotherapy, together with surgery, has been the mainstay treatment in the management of patients



with glioblastoma since the 1970s and the combination of both doubles overall survival in patients with malignant gliomas.<sup>23,24</sup> Little clinical progress was made over the past decades. The prognosis of patients with glioblastoma remains poor with median survival of ~14 months after adjuvant temozolomide-based radiochemotherapy<sup>2,25</sup> with relevant predictive impact of inactivation of the methylguanine DNA methyltransferase gene promoter.<sup>26</sup> Local recurrence within 2.0 cm of the pre-surgical initial tumor margin is the main pattern of failure following treatment of glioblastoma;<sup>27,28</sup> a biomarker helping to dissect responding patients is missing. Delineation of target volumes by metabolic imaging and more sophisticated MRI techniques with focus on tumor areas with a need for higher doses or better sparing of sensitive structures is in the center of most research to optimize radiotherapy. A second pillar with little news to report is the assessment of radiosensitizers. The third aspect at least in sites with the respective technical prerequisites is the emergence of heavy ion radiotherapy using carbon ions (CIR) and raster scanning technique demarcating a landmark development in the field of high precision radiotherapy.<sup>28</sup> High precision radiotherapy holds the promise in escalating the dose in the tumor and improving local control while sparing normal tissue.<sup>26</sup> However, previous data indicate that escalating the dose alone will not suffice to improve outcome in these radioresistant tumors in the clinic. Conceptually, precision radiotherapy is an effective therapy with intrinsic limitations in highly infiltrative disease. In our view, more weight may be put on integrating radiotherapy into current biological concepts, for example, into immunotherapy, for example, by understanding 'remote', so-called abscopal (bystander) effects.<sup>29</sup> As already discussed in the surgery section, implementation of novel radiation qualities or planning strategies would require controlled trials. Similarly, it is surprising to realize that despite many thousand patients being treated each year with radiation, molecular biomarkers to predict response are still lacking.<sup>30,31</sup>

### Chemotherapy

To date, the landmark contribution of the European Organization for Research and Treatment of Cancer (EORTC) with the EORTC 26981 trial defines the standard of chemotherapy, that is concomitant treatment with temozolomide at 75 mg/m<sup>2</sup> body surface, on empty stomach approximately 2 h prior to the radiotherapy

session and fasting in the mornings or later after breakfast of nonradiation days. Adaption is made with treatment pauses according to blood counts and a *Pneumocystis jirovecii* pneumonia prophylaxis is recommended especially in lymphocytopenic individuals. There is a 4-week break and the chemotherapy is completed by six maintenance cycles of temozolomide on 5 out of 28 days at 150 mg (cycle 1) and at 200 mg (cycles 2–6)/m<sup>2</sup> body surface adapted according to general and more specifically hematological tolerance.<sup>2,25</sup> Again, supportive measures may include a PCJ prophylaxis and an antiemesis. Steroid use is regarded a negative factor for the efficacy of treatment.

Neither the adaption of the schedule, for example, 21/28 days or 7/14 days temozolomide in the maintenance phase<sup>32,33</sup> nor the longer exposure<sup>34</sup> has a proven impact to date.

### Impact of molecular diagnostics

According to the most recent adaption of the WHO classification, *MGMT* promoter methylation is predictive for efficacy and response to alkylating and methylating chemotherapy agents<sup>2,26</sup> in glioblastoma. Long-term surviving patients have >90% glioblastoma with methylated *MGMT* promoter<sup>2</sup> versus 35% in the general glioblastoma patient population.<sup>35</sup>

*IDH1/2* mutations are relevant positive prognostic factors and in glioblastoma strongly associated with glioblastoma progressive from a lower grade glioma.<sup>36</sup> The existence of *de novo IDH*-mutated glioblastoma is a topic of controversy.

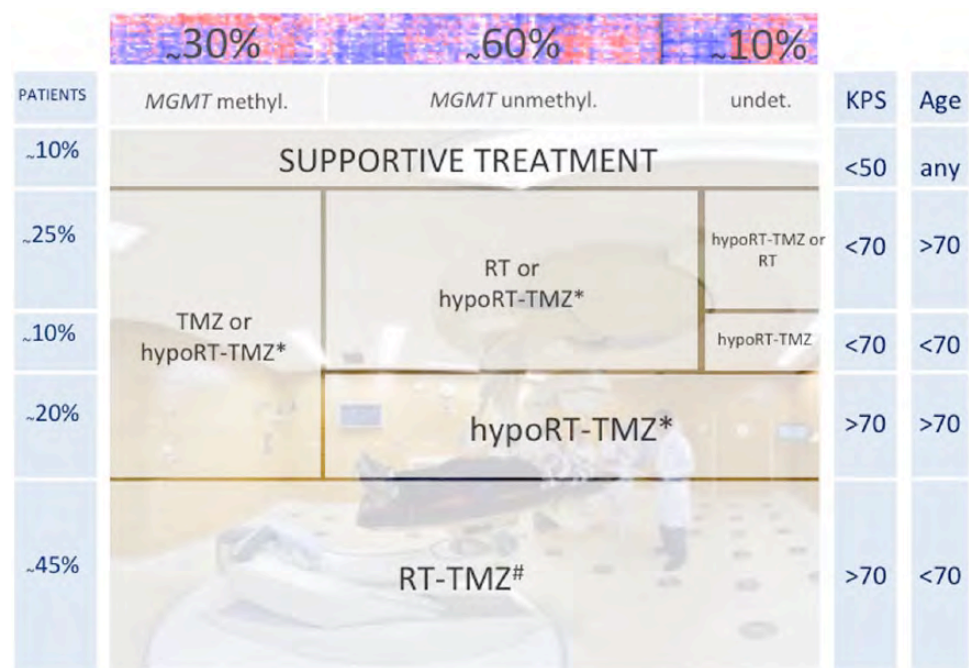
There is no consistent correlation of EGFR amplification with survival, largely irrespective of the age at clinical manifestation. The variant III of EGFR seems to get lost in the progression at least of a fraction of patients.<sup>37</sup> Loss of heterozygosity (LOH) 10q is the most frequent genetic alteration in glioblastoma and is associated with reduced survival. The presence of PTEN mutations is not associated with prognosis of glioblastoma patients.<sup>17,38</sup>

### Adaptions/options to the standard in newly diagnosed patients

#### Elderly patients

The Scandinavian Neuro Oncology Network, the Neurooncology Working Group of the German





**Figure 1.** Therapy options and recommendations for patients with glioblastoma in different age groups according to Karnofsky performance status.<sup>41</sup> Prevalence (according to CBTRUS, 1) is depicted by the size of the boxes (adapted from Wick and colleagues, 2018).<sup>42</sup>

Cancer Society (NOA) as well as the CCTG (Canadian Cancer Trials Group) and the EORTC have provided randomized data for the treatment of elderly patients with glioblastoma. These trials provide evidence that hypofractionated radiotherapy over 3 weeks is equivalent to longer treatment and that chemoradiation using that shorter radiotherapy with temozolomide as well as maintenance temozolomide is superior to radiotherapy alone.<sup>39</sup> In the absence of comparative data between regular fractionated and hypofractionated chemoradiotherapy as well as a lack of these data compared with temozolomide alone leaves room for individualized treatment decisions based on clinical assumptions, but not data. Today, increased age (>65/70 years), relevant comorbidities, Karnofsky performance status (<70) and some considerations on frailty are used to provide guidance (Figure 1). Molecular testing is of some help. It has revealed a low prevalence of favorable prognostic markers in elderly patients.<sup>40</sup> The virtual absence of IDH mutations in patients over the age of 65, according to the new WHO classification, suggest that differential prognosis is not based solely on age but rather that separate entities exist with a distinct age distribution.<sup>38</sup> The prevalence of *MGMT* promoter methylation is

similar to that in younger patients. Specifically, in the elderly patients a string call was made for the use of *MGMT* as a predictive biomarker.<sup>26,39</sup>

Treatment according to *MGMT*

Current (European) guidelines are explicit that only in elderly or frail patients the use of temozolomide can be adapted according to the methylation of the O6-methylguanine DNA methyltransferase gene promoter. Otherwise, *MGMT* testing though performed with increasing frequency has no practical impact in the management of patients. Some centers take recent data on the *MGMT*-dependence of response to temozolomide<sup>43</sup> or lomustine<sup>44</sup> at glioblastoma progression as decisive to not expose patients again to alkylating or methylating chemotherapies at progression, but this concept is neither generally supported nor explicitly stated in our guidelines. Trials in patients without *MGMT* promoter methylation<sup>26</sup> showed that leaving out temozolomide from first-line treatment was of no detriment to patients, challenging the view that temozolomide should be used in every patient despite the absence of *MGMT* promoter methylation. Recent data might further help to decipher



the benefitting patient population. TERT expression may be necessary to ensure the *MGMT* methylation related benefit to alkylating chemotherapy.<sup>45</sup> Overall, *MGMT* status testing without taking consequences is unsettling for patients, creates a lot of second consulting and finally undermines trust in our profession. On the other hand, testing offers the opportunity to safe patients a treatment with no or little chances for help plus offers options for alternatives, which should be based on further precision measures by looking for molecular lesions potentially relevant for targeted or immunotherapies (see Outlook). This should be avoided in patients <70 years without the patient-physician team willing to take any consequences.

### Use of tumor-treating fields

Tumor-treating fields (TTFields) use alternating electrical fields to inhibit mitoses *via* disruption of the spindle apparatus. In a randomized trial that was published originally in *JAMA*, the addition of TTFields to standard radiotherapy (RT) and temozolomide (TMZ) in newly diagnosed glioblastoma extended overall survival [hazard ratio (HR), 0.64 (99.4% confidence interval (CI), 0.42–0.98);  $p = 0.004$ ].<sup>46</sup> The effect of the fields is maintained at long-term (final) analysis,<sup>47</sup> though the selected patient group, the lack of a control for the more active supportive care and the relatively small difference in long-term survival at 5 years compared with the EORTC trial<sup>2</sup> raised questions in the ‘expert’ community. Whether the magnitude of overall survival increase outweighs the individual burden and the societal cost is yet to be determined. The long-term relevance of the fields will be determined by whether they are routinely integrated into daily practice and the success (or not) of other concepts discussed below.

## Concepts at recurrence

### Re-surgery

As already stated above, we might consider reoperation to improve symptoms, in the case of early progression in patients in whom initial surgery was not adequate or later progressors, when the initial treatment might just be repeated. We are uncertain about the effect of second surgery on overall survival. It is considered that another gross total resection of enhancing tumor<sup>48</sup> is relevant,

but prospective controlled data are lacking. Recently, there is an increasing demand for post-progression tissue extraction as targeted treatments may offer valid options and also therapy with checkpoint inhibitors<sup>49</sup> should be restricted to patients with the most likely benefit.

### Re-radiotherapy

The efficacy of re-irradiation is uncertain until date. Its appreciation varies between sites, countries, recurrence pattern and with the time interval to the first treatment. Fractionation depends on tumor size. Fractionation between 2.0 and 2.4 Gy has been tested, but also higher doses per fraction of 5–6 Gy using stereotactic hypofractionated radiotherapy to a total dose of 30–36 Gy, and also radiosurgery with a single dose of 15–20 Gy. Overall toxicity seems not to be the main issue.<sup>50</sup> As with systemic therapies, there is a lack of relevant efficacy, for example, progression-free survival rate of 3.8% at 6 months in the APG101 randomized trial at 18 fractions of 2 Gy.<sup>51</sup> There is a clear need of a definition for a population candidate for re-irradiation, research on biomarkers involved in radioresistance<sup>52</sup> and also trial concepts that provide controlled information on whether or not this is a reasonable approach. The aforementioned applies to conventional photon therapy and may or may not be challenged if different radiation qualities, like C<sup>12</sup> ions or protons are being used.

### Chemotherapy at progression

Most studies at progression are of limited size therefore impacted by the heterogeneity of the disease, non-comparative or fail to use a control arm lacking the experimental drug. In addition to re-exposure to temozolomide at standard dose, most patients will receive one of the nitrosoureas, that is, carmustine (BCNU), lomustine (CCNU), or fotemustine. They alkylate at the N<sup>7</sup> and O<sup>6</sup> positions of guanine and introduce interstrand crosslinks as well as act by carbamoylation of amino acids interfering with transcriptional, translational and posttranscriptional processes.<sup>53–56</sup> These are DNA alkylating and methylating agents that cross the blood–brain barrier and have been extensively used in glioma treatment. They may induce considerable hematological toxicity with long-lasting bone marrow suppression, liver and renal toxicity, and, specifically carmustine, interstitial lung disease. Efficacy is dependent on *MGMT* status both in the



AVAREG trial<sup>57</sup> and also in the EORTC 26101 trial.<sup>44</sup> At the same level, temozolomide re-exposure is only meaningful if patients are diagnosed with a progressive glioblastoma harboring a methylated *MGMT* promoter.<sup>43</sup> It may be extrapolated from the BR12 trial that used standard dose and dose-intensified temozolomide after radiotherapy alone (and not re-challenge after temozolomide)<sup>58</sup> and the dose-dense maintenance treatment of RTOG 0525<sup>32</sup> that conventional (5 out of 28 days) chemotherapy is not inferior to any dose-intensification<sup>43</sup> and the latter may not be used unless new data appear.

#### *Experimental options at progression*

Certainly, many treatments can be tried in patients with progressive glioblastoma after the above mentioned. As present, we would recommend trial participation. Also, performance status and the general situation are impacting options. In the United States, bevacizumab is approved and may offer a further treatment line with the promise of prolonging progression-free survival and potentially in selected patients also overall survival. In the European Union, this option is very restricted due to a lack of approval. Here, we recommend a pragmatic approach that involves obtaining post-progression tissue and assess for potential molecularly informed treatment decisions.<sup>59</sup> The fields although sometimes advertised differently did not hold the promise at progression therapy.<sup>60</sup>

### **Outlook**

#### *Antiangiogenesis*

After the failure of bevacizumab to demonstrate an effect on overall survival in newly diagnosed patients,<sup>61</sup> the subsequent randomized, phase III EORTC 26101 compared lomustine with or without bevacizumab at progression. Despite prolonging progression-free survival (HR 0.49; CI 0.39, 0.61), combined lomustine and bevacizumab treatment does not confer an overall survival advantage (HR 0.95; CI 0.74, 1.21;  $p = 0.650$ ) over treatment with lomustine alone in patients with progressive glioblastoma.<sup>44</sup> In this study, crossover to bevacizumab occurred in 35.5% of patients in the control arm; whereas 18.7% of patients in the combination arm continued bevacizumab at progression. However, bevacizumab

continues to play a role in the treatment of glioblastoma in large areas of the world. Many practicing clinicians regard its positive effect on progression-free survival, and other palliative effects, and neurological improvement seen in many patients as meaningful benefits, in the absence of any overall survival gain in the entire patient population. Pragmatically, bevacizumab with its documented beneficial effect on radionecrosis-related edema and neurological dysfunction<sup>62</sup> might be particular interesting for patients with radiological and clinical deterioration, frequently called 'pseudoprogression'.

#### *Immunotherapy*

Immunotherapy is regarded a valid option for patients with glioblastoma though data to prove this hypothesis are largely confined to case reports and by analogy to the successes in other malignancies. Independent of the approach (e.g. checkpoint inhibition, targeted vaccine, adoptive T-cell transfer), the clonal representation of the target antigen and the immunosuppressive microenvironment have to be taken into account for clinical development. For instance, EGFR vIII is a subclonal antigen with heterogeneous expression in the tumor tissue, which may, in theory, be subjected to immune evasion. Despite promising initial data, a large phase III trial failed.<sup>37</sup> VXM01 is encoding vascular endothelium growth factor receptor 2 (VEGFR2) in order to evoke an immune response specifically directed against the tumor vasculature. It is currently in clinical development as a treatment for solid cancer types. The oral T-cell vaccine platform of the company VAXIMM is based on the approved, live attenuated *Salmonella typhi* vaccine strain Ty21a, which has been applied in millions of individuals for prophylactic vaccination against typhoid fever.<sup>63</sup> IDH1R132H<sup>64</sup> and H3.3K27M<sup>65</sup> as early founder mutations represent clonal antigens, but controlled clinical data on their relevance are yet to be generated. The Glioma Actively Personalized Vaccine Consortium (GAPVAC) realized an immunotherapy, for which the selection of actively personalized peptide vaccines (APVAC) for treatment of newly diagnosed glioblastoma was based not only on whole-exome sequencing but also on human leukocyte antigen (HLA)-ligandome analyses providing information of the actual presentation of relevant epitopes in the tumor. Mutated peptides identified by next



generation sequencing and mass spectrometry may not only be used for peptide vaccination, but serve as a platform for personalized immunotherapies with potentially more aggressive cell-based treatments. Controlled clinical trials assess the efficacy of nivolumab in progressive and newly diagnosed glioblastoma. Whereas the trials in newly diagnosed patients separated according to *MGMT* promoter methylation status are ongoing, results from the study in progressive glioblastoma comparing nivolumab and bevacizumab have been reported. A total of 369 patients, progressive after standard of care, were randomized to nivolumab 3 mg/kg every 2 weeks ( $n = 184$ ) or bevacizumab 10 mg/kg every 2 weeks ( $n = 185$ ). Progression-free survival was superior in the bevacizumab arm (HR = 1.97; 1.57, 2.48) with medians of 3.5 months (2.9, 4.6) and 1.5 months (1.5, 1.6), respectively. There was no signal for any difference in overall survival in this unselected patient population (HR=1.04; 0.83, 1.30;  $p=0.76$ ) with medians of 10.0 months (9.0, 11.8) for bevacizumab and 9.8 months (8.2, 11.8) for nivolumab.<sup>66</sup> Nivolumab or temozolomide in combination with radiotherapy in newly diagnosed patients with *MGMT*-unmethylated glioblastoma are treated in CheckMate 498. CheckMate 548 assesses nivolumab or placebo in combination with radiotherapy and temozolomide in patients with *MGMT*-methylated or indeterminate glioblastoma at first diagnosis. These trials also do not enrich for patients more likely to benefit from the immune intervention.<sup>67</sup>

Checkpoint inhibitors in glioblastoma may work only with a specific immunogenic background, potentially to be defined by MSI-H or dMMR, or with associated treatment, for example, vaccination. The most prominent checkpoints in other malignancies may not be the most relevant in glioblastoma;<sup>68</sup> other factors like the CD95 system, tryptophan-2,3-dioxygenase (TDO)<sup>69,70</sup> or other programmed death family members<sup>71</sup> may be of greater importance. In addition to being restrictive based on molecular stratification, there are concepts in development that promise a stronger immunoeffect. Several chimeric antigen receptors are in clinical development for glioblastoma. The currently available data are for interleukin 13 receptor (IL13R)- $\alpha$ 2, EGFR variant III, and HER2 as targets. There are already cases and small series showing feasibility of delivery and manageable toxicity,<sup>72</sup> but

translational research regarding efficacy and resistance mechanisms are ongoing.<sup>73,74</sup>

### Targeted treatments

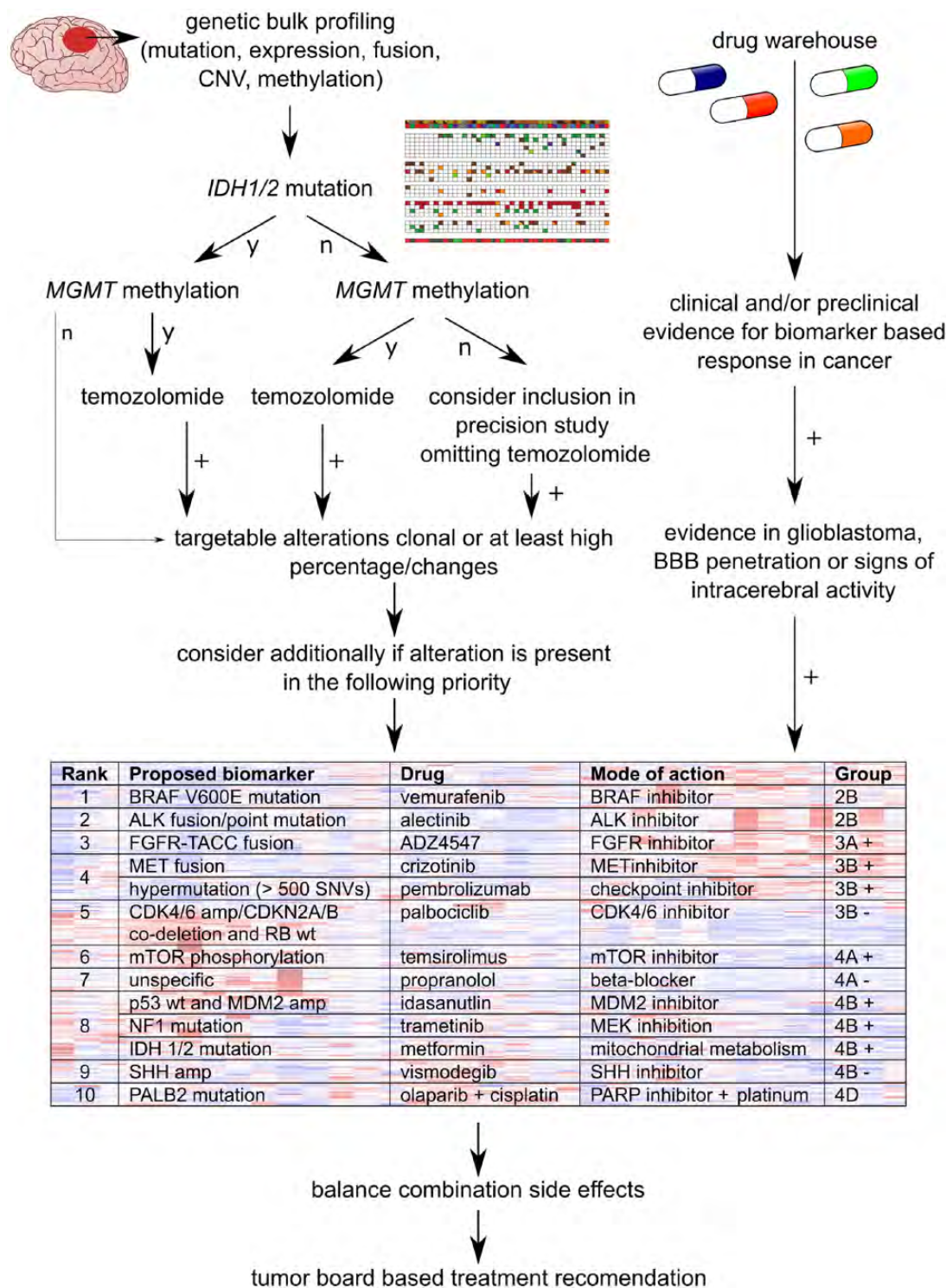
Biomarkers that predict response and ultimately benefit from a given therapy plus an effective treatment are the cornerstones of precision neuro-oncology. *MGMT* is a good example for a predictive biomarker in the field of gliomas.<sup>26,41</sup> However, no officially accepted (accredited) test exists. Further, it is possible that predicting response to temozolomide is more complex than by just determining *MGMT* methylation status. The delineation of the right subgroups may also involve global methylation profiles and TERT status.<sup>75,5</sup>

Please find a strategy for treatment of newly diagnosed or recurrent glioblastoma and examples of putative predictive biomarkers in Figure 2. Importantly, the prerequisite until now is a tissue sample from the tumor that needs treatment (and not just archival information).

Further, there are interesting examples of drug repurposing with less intuitive compounds for the glioblastoma field. Also, these compounds may deserve testing in an otherwise difficult clinical situation and with indicative biomarkers associated (Table 1). In a pilot series that serves as model for the examples provided in the current review, compounds were recommended in combinations, following the concept that blocking multiple pathways with combination therapy may be more effective than single agent therapy especially when treating recurrent, progressive glioblastoma.<sup>59</sup>

Therefore, well-considered allocation of newly diagnosed as well as progressive patients to clinical trials based on molecular characteristics of the tumor as well as necessary retrospective validation of potential biomarkers are essential in a clinical setting. A current concept prospectively using biomarkers to enrich for potentially benefitting patients is the Nationales Centrum für Tumorerkrankungen (NCT) Neuro Master Match (N<sup>2</sup>M<sup>2</sup>), a trial of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without *MGMT* promoter methylation.<sup>76</sup> The Glioblastoma Adaptive, Global, Innovative Learning Environment (AGILE) consortium is planning to take a differential approach by reassessing potential





**Figure 2.** Sketch to show a way towards precision. Putative work flow from a glioblastoma tissue sample. BBB, blood-brain barrier; CNV, copy-number variation; GBM, glioblastoma; IDH, isocitrate dehydrogenase; MGMT, O6-methylguanine DNA methyltransferase; n, no; y, yes.

biomarkers from an unselected cohort with given therapies first and integrating these information via adaptive processes to enrich while the trial accrues.<sup>77</sup>



**Table 1.** Options for molecular adapted treatments [according to Byron and colleagues and Pfaff and colleagues].<sup>59,76</sup>

Molecular lesion	Signaling pathway	Potential therapy
Neurofibromatosis 1 (NF1) gene alteration	MEK	Trametinib
Loss of partner and localizer of BRCA2 (PALB 2) or BRCA	PARP	Olaparib and cytotoxic agent
IDH mutation	IDH - methylation	Alkylating agents, demethylating agents (5-azacytidine, decitabine), metabolic agents (metformin)
MutS protein homolog (MSH)6, MSH4, MSH5, postmeiotic segregation increased (PMS)1, PMS2, MutL homolog (MLH)1, and MLH2 mutations or hypermutator phenotype, DNA polymerase epsilon catalytic subunit (POLE) mutation	Checkpoint inhibition	Pembrolizumab, nivolumab
Proneural (IDH-wildtype) expression pattern	Anti-VEGF	Bevacizumab
Lower levels of methylation of the CpG2 in the promoter of the CD95 ligand	CD95/CD95ligand	Asinercept
IDH, isocitrate dehydrogenase; MEK, mitogen-activated protein kinase; PARP, poly(ADP-ribose)-polymerase; VEGF vascular endothelial growth factor		

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## Conflict of interest statement

The authors declare that there is no conflict of interest.

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# Alternating Electric Fields Therapy for Malignant Gliomas: From Bench Observation to Clinical Reality

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## Abstract

Alternating electric fields of intermediate frequencies, also known as Tumor Treating Fields (TTFields or TTF) is a novel anticancer treatment modality that disrupts tumor cell mitosis at the metaphase–anaphase transition, leading to mitotic catastrophe, aberrant mitotic exit, and/or cell death. It is realized through alteration of the cytokinetic cleavage furrow by interference of proteins possessing large dipole moments, like septin heterotrimer complex and  $\alpha/\beta$ -tubulin, and that results in disordered membrane contraction and failed cytokinesis. Aberrant mitotic exit also elicits immunogenic cell death, which may potentiate an immune response against treated tumors. Notably, in patients with recurrent glioblastoma multiforme (GBM) a prospective clinical trial demonstrated comparable overall survival and progression-free survival after TTFields therapy and best physician's choice chemotherapy. Moreover, it was shown that in patients with newly diagnosed GBM initially treated with standard chemoradiotherapy with daily temozolomide (TMZ), adjuvant TTFields combined with TMZ offered better survival than adjuvant TMZ alone. Therefore, TTFields therapy can be appreciated as a standard treatment option in cases of intracranial malignant gliomas, whereas future studies should establish its optimal combination with other existing anticancer modalities, which may offer additional survival benefits for patients.

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## Introduction

Exposure of cells to non-ionizing, alternating electric fields can have different consequences depending on the frequency. For instance, at frequencies of 1 kHz or lower, it causes depolarization of the membrane potential in excitable cells, such as neurons, cardiac myocytes, and muscle cells, via the opening of voltage-gated ion channels [1–3]. Defibrillators and electroshock therapy both rely on the ability of low frequency, high



intensity electric fields to induce membrane depolarization. On the other hand, within a narrow range of intermediate frequencies (with a peak activity at 100–200 kHz) alternating electric fields, also known as Tumor Treating Fields (TTFields or TTF), are able to perturb cancer cells during mitosis, affecting their physiology by the induction of minute forces on intracellular proteins possessing high dipole moments [4].

Both experimental models and clinical studies in patients with glioma demonstrated that TTFields therapy resulted in tumor regression [5–7]. Based on favorable data from a phase III clinical trial a device designed to deliver such treatment in humans, the NovoTTF-100A (Optune®; NovoCure Ltd., Haifa, Israel), has been approved by the US Food and Drug Administration (FDA) for management of recurrent glioblastoma multiforme (GBM) [8, 9]. Furthermore, analysis of a second phase III trial has shown that in patients with newly diagnosed GBM initially treated with standard fractionated radiotherapy (FRT) concomitant with daily temozolomide (TMZ), adjuvant TTFields therapy combined with TMZ offers better survival than adjuvant TMZ alone [10].

### Basic Mechanisms of TTFields Therapy

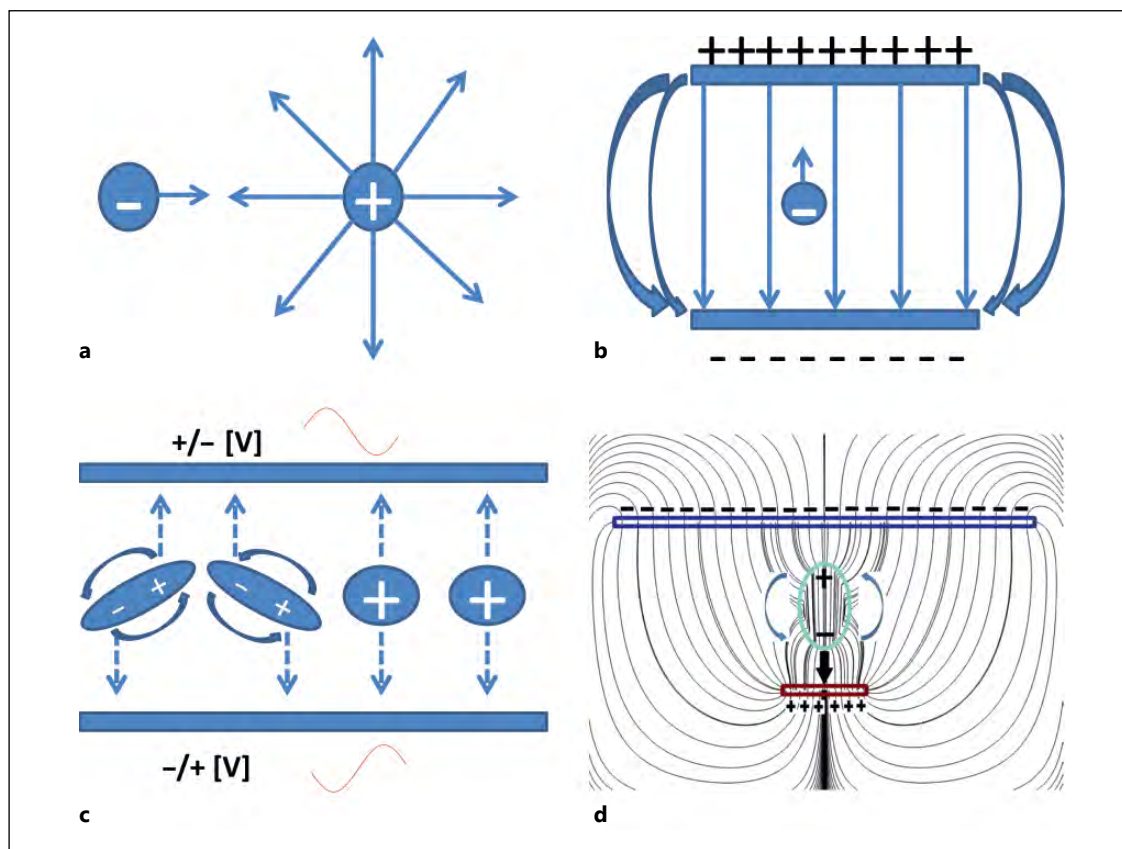
The basic mechanisms of chemotherapy and irradiation usually involve triggering G1/S or G2/M cell cycle checkpoints, as well as spindle poisons mediating a block in metaphase by initiating the spindle assembly checkpoint. By contrast, the cells exposed to TTFields during mitosis showed normal entry into metaphase, but exhibited random and uncontrolled violent plasma membrane blebbing that coincided with metaphase exit [4, 5].

#### *Induction of a Mechanical Force on Protein Dipoles*

Most intracellular proteins do not have static point charges. Instead, they possess dipole moments produced by discontinuities of the exposed charges on their surfaces arising from charged amino acid moieties or bound nucleotides. The size of the dipole moment of a protein is a function of the magnitude of negative and positive charge separation and the distance between the differentially charged regions.

In a static electric field, positively charged molecules will migrate toward the negatively charged pole, while a negatively charged molecule will migrate towards the positively charged pole. This behavior differs in an alternating electric field, since any movement in one direction will be canceled out when the field switches polarity. However, even though there is no net translational movement, alternating changes in the electric fields polarity can induce rotational or torsional movements of molecules possessing dipoles (Fig. 1). In this way, TTFields of intermediate frequency probably produce stresses on certain proteins possessing high dipole moments and impact their intracellular function [11]. These properties most likely constitute the basis for the cellular disruption seen during mitosis in exposed cell cultures, characterized by induced violent plasma membrane blebbing and leading to cell death [4, 5].





**Fig. 1.** Behaviors of point charge and dipole in static and alternating electric fields. When it encounters a point source, a negative point charge migrates toward a positive source (a). In a parallel plate, a negative point charge migrates toward the positive plate (b). When point charges are exposed to alternating electric fields there is no net translational movement, but for dipoles there are rotational or torsional movements that vary according to the frequency of time-varying electric fields (c). When a dipole is exposed to a time-varying, non-uniform electric field (dielectrophoresis [d]), there are both translational and torsional movements.

### *Alterations of Mitotic Function during Cytokinesis*

Mitosis is a meticulously orchestrated event wherein various structures being rapidly and precisely assembled to function as cells progress from prometaphase to telophase and then to daughter cell formation. All of these cellular machineries must be executed with both temporal and spatial precision, which also creates its potential vulnerability to various perturbations. The observation that TTFs disrupt cells during mitosis [4, 5] strongly suggested their interaction with one or more processes critical to cell division.

During preparation for mitosis, the replicated centrioles migrate towards the opposite poles of the dividing cell. As mitosis proceeds, they nucleate microtubules that form the metaphase spindle radiating towards and meeting near the cell's equatorial



center. The condensed chromosomes migrate along the spindle microtubules until they reach this midpoint, forming the mitotic (metaphase) plate. Later, the paired kinetochores on each sister chromatid capture the ends of microtubules within opposing metaphase spindles. This acts to not only align the constituent chromatids of each chromosome towards the poles of the forming daughter cells, but also creates tension across the kinetochores. Tensionless kinetochores produce a signal that acts on the E3 ubiquitin targeting subunit of cell-division cycle protein 20 (Cdc20) of the anaphase-promoting complex, also called the cyclosome (APC/C<sup>Cdc20</sup>). Cdc20 exists in either an active or inactive form and the signal from tensionless kinetochores favors the inactive conformation. Since a single uncaptured kinetochore produces sufficient signal to prevent APC/C<sup>Cdc20</sup> activation, metaphase exit only proceeds after the last chromatid is captured. Upon activation, APC/C<sup>Cdc20</sup> targets the ubiquitin-mediated destruction of proteins, including cyclin B and securin, which maintain cells in metaphase [12, 13]. Once these proteins are destroyed, cells irrevocably proceed into anaphase [12, 14–17] and cytokinesis [18].

The cytokinetic cleavage furrow (CCF) formed by anaphase spindles between the separated chromosomes creates coordinated forces necessary for division of the parental cell. Separation of the daughter cells is the result of ingression by the CCF and its constriction around the equatorial fission plate, which is driven by non-muscle myosin II (NM II) activity [19–21]. The anaphase spindle midline contains proteins that are critical for proper CCF localization and function [22–25]. Centralspindlin complex (composed of KIF23 and MgcRacGAP dimers) recruits the structural domain of guanine nucleotide exchange factors (RhoGEF) of the epithelial cell transforming 2 (ECT2) protein early in anaphase [26] from where it is subsequently and rapidly delivered to the CCF [27]. ECT2 then binds the adaptor protein anillin, which in turn binds to both the septin 2, 6, and 7 (SEPT2-SEPT6-SEPT7) heterotrimer [28] and NM II. Together, these proteins cooperate in the recruitment, localization, and regulation of the contractile elements within the CCF responsible for producing the forces necessary for cytokinesis. The septin complex plays a critical role in demarcating the lateral boundaries that limit NM II activation to the equator of the cell above the fission plate, constraining its contraction to the CCF [29]. In addition, ECT2 protein has been shown to be required for the stability of the anaphase spindle midline, which becomes disordered upon its depletion in mRNA knockdown experiments [30].

Our studies of cells treated with TTFields did not demonstrate differences in mitotic progression through either prometaphase or metaphase, or in the rates of cyclin B and securin degradation, findings that suggest normal capture of microtubules by kinetochores. However, the timing of the violent membrane blebbing was consistent with the timing of metaphase exit [4]. These data indicate that TTFields affect cells within the metaphase-anaphase transition and strongly suggest that membrane blebs are likely the result of plasma membrane rupture from cell surface cytoskeleton. These observations have significant implications on the clinical use of TTFields in cancer treatment. Unlike other therapies that induce damage triggering the G1/S, G2/M, or



spindle assembly checkpoints, alterations of the cellular machineries after they have committed to anaphase are not correctable and invariably lead to mitotic catastrophe, aberrant mitotic exit, and cell death [18]. Since there is little overlap between the effects of TTFields and the mechanisms of action of most other available anticancer therapies, combined treatment strategies are readily possible.

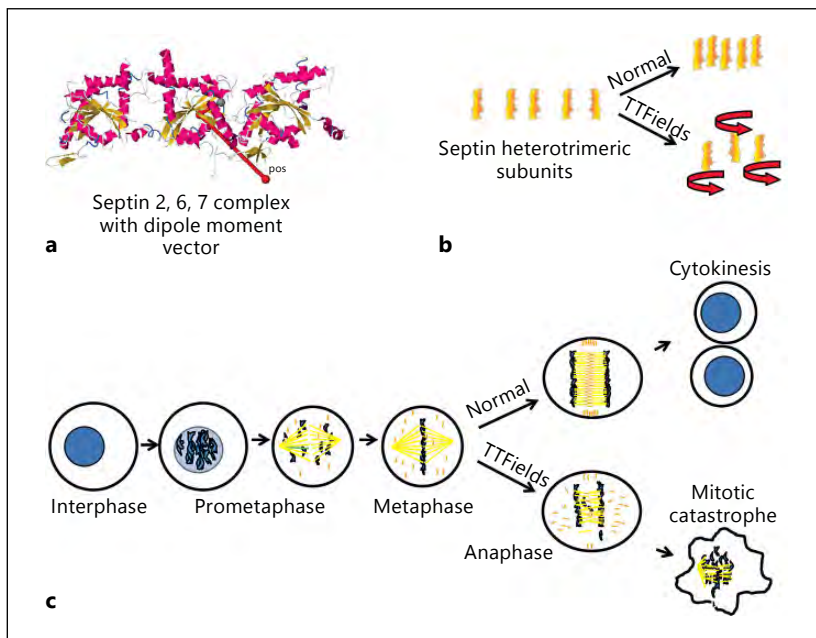
### *Molecular Targets of TTFields*

As mentioned above, TTFields are likely to affect molecular targets that possess sufficiently high dipole moments and are needed for the proper functioning of the CCF. The SEPT2-SEPT6-SEPT7 complex [31] has a very high dipole moment of 2711 debyes (D), and it has a directional vector that is orthogonal to the longitudinal axis of the heterotrimer. For comparison, this dipole moment is 5 standard deviations greater than the median value of 542.66 D for intracellular proteins [32]. Given the critical role of SEPT2-SEPT6-SEPT7 complex in regulating CCF function and its large dipole moment, we considered it as a potential target for TTFields action (Fig. 2). Of note, knockdown of SEPT6 or SEPT7 also results in CCF dysfunction leading to violent membrane blebbing and aberrant mitotic exit [29, 33].

The SEPT2-SEPT6-SEPT7 heterotrimers align parallel to each other along longitudinal axes of the anaphase spindle midline and CCF [31, 34–36]. Since the direction of dipole moment vector is orthogonal to this axis, TTFields predictably induce rotational or torsional movement around it, preventing the assembly of the higher-order septin structures. Analysis of septin localization in anaphase showed a significant decrease in anaphase spindle and CCF accumulation in cells treated with TTFields, demonstrating that this therapy is able to alter septin behavior during mitosis. In addition, anaphase spindle midlines were shown to be disordered, which may play a major role in producing the observed catastrophe during anaphase. It is unclear, however, whether the CCF perturbation is the result of the disordered anaphase spindle midline, the failed recruitment of septin to CCF, or both. Nevertheless, these data support a model in which perturbation of septin function by TTFields during anaphase results in membrane blebbing and that disrupts the dividing cell.

The  $\alpha/\beta$ -tubulin dimer, which also has a high dipole moment of 1660 D, represents another possible therapeutic target of TTFields. It supports an alternative hypothesis for the disordering of the anaphase spindles, which proposes that rapid microtubule dynamics may make this spindle more vulnerable to disruption at the level of microtubule polymerization [4]. Since astral microtubules help in delivering and/or controlling small GTPase RhoA (Ras homolog family, member A) activity within the CCF [30, 37], TTFields could produce sufficient disruption of microtubule dynamics that alters the delivery of these components and thus contributes to the induction of CCF dysregulation. While our experiments did not demonstrate gross differences in microtubule structures in fixed metaphase or spreading cells, it is possible that therapy-induced perturbations of microtubules during mitosis were undetectable.





**Fig. 2.** Mechanism of action in septin-based model of TTFields therapy. Septin 2, 6, and 7 heterotrimer (a) possesses a dipole moment of 2711 D, which is 5 standard deviations greater than the average for intracellular proteins. The directional vector of this dipole is orthogonal to the longitudinal axis of the complex and TTFields can induce rotation around this axis (b). This interfere with the formation of the higher-order septin structures required to complete mitosis. During mitosis (c), cells experience nuclear envelope breakdown and chromosome condensation (blue) in prometaphase, with further formation of the metaphase plate by chromosome congression to the midpoint of the metaphase spindle (yellow). During anaphase, septin 2, 6, and 7 heterotrimers normally localize to the anaphase spindle midline and cytokinetic cleavage furrow (CCF) to support their stability and function. Perturbation of normal CCF assembly by TTFields results in mitotic catastrophe, leading to aberrant mitotic exit followed by cell death.

Finally, given the vulnerability of cells to disruption during mitosis, other proteins, in addition to septin and  $\alpha/\beta$ -tubulin, may also be affected by TTFields. The alteration of multiple different protein species in aggregate might be required to produce the violent membrane blebbing observed in exposed mitotic cells.

### *Apoptosis and Immunogenicity*

Aberrant mitotic exit induced by TTFields can potentially lead to cell death, which is likely caused by an unresolved mitotic spindle apparatus, multiple centrioles, and/or the presence of supernumerary chromosomes [4, 38]. According to our data, G0/G1 cell cycle arrest and increased rates of apoptosis are observed within 36 h of exposure to TTFields, which indicates that cells exiting mitosis following treatment are significantly deranged and suggests that the clinical efficacy of this therapy may somewhat depend on tumor genetics.



There are at least two known forms of programmed cell death [39]. The first one, homeostatic apoptosis, leads to an orderly cell death resulting in the production of plasma membrane blebs that create small cell fragments ready for removal by phagocytes. Such cellular fragments also suppress the inflammatory effector functions by simultaneously upregulating phosphatidylserine (Ptd-L-Ser) on the cell surface, which limits immune damage during wound healing or organogenesis. In contrast, the second form, known as immunogenic cell death (ICD), acts similarly to the early immune defense against viral infection. It also results in Ptd-L-Ser exposure on the cell surface, but can elicit an active immune response against the dying cell through expression of the endoplasmic reticulum chaperone calreticulin [40] and secretion of both ATP and high mobility group box 1 (HMGB1) protein [39]. Calreticulin promotes phagocytosis by innate immune cells, while ATP and HMGB1 protein act as chemotactic factors that activate immune effectors and stimulate antigen presentation function [39].

Aberrant mitotic exit elicits ICD [41]. Moreover, cells treated with TTFields demonstrated increased surface expression of calreticulin and depletion of the intracellular HMGB1 protein, indicating its secretion. Thus, such treatment may induce an antitumor immune response, which is supported by the finding in *in vivo* cancer metastasis models that short application of TTFields therapy resulted in a lower rate of metastasis and increased immune infiltration within residual neoplastic lesions [6]. These data have profound clinical implications, as they suggest that combining TTFields therapy with immunotherapy may provide added benefit for cancer patients.

### Distribution of TTFields within the Brain

The NovoTTF-100A device delivers TTFields via two pairs of transducer arrays arranged in an orthogonal fashion on the patient's head (Fig. 3) [42]. Each array consists of 9 ceramic disks connected to a generator and a battery pack. Patients should ideally achieve compliance to treatment of  $\geq 75\%$ , i.e.,  $\geq 18$  h per day.

Computer modeling can provide non-invasive estimation of electric field distribution from the surface arrays on the scalp into various brain structures and into the tumor volume. For this purpose co-registration of MR images and automated or manual segmentation of the different intracranial tissues is performed, known dielectric properties are assigned to each of the segmented tissue types, and ceramic disks from the arrays of the NovoTTF-100A system are placed onto the scalp to build a composite mesh model with various geometries. This model is then imported into finite element modeling software to solve for the electric field distribution, provided that the necessary parameters of tissue dielectric properties are assigned appropriately. The final finite element solution consists of 2-dimensional (2D) plots of the brain shown in axial, coronal, and sagittal planes (Fig. 4).

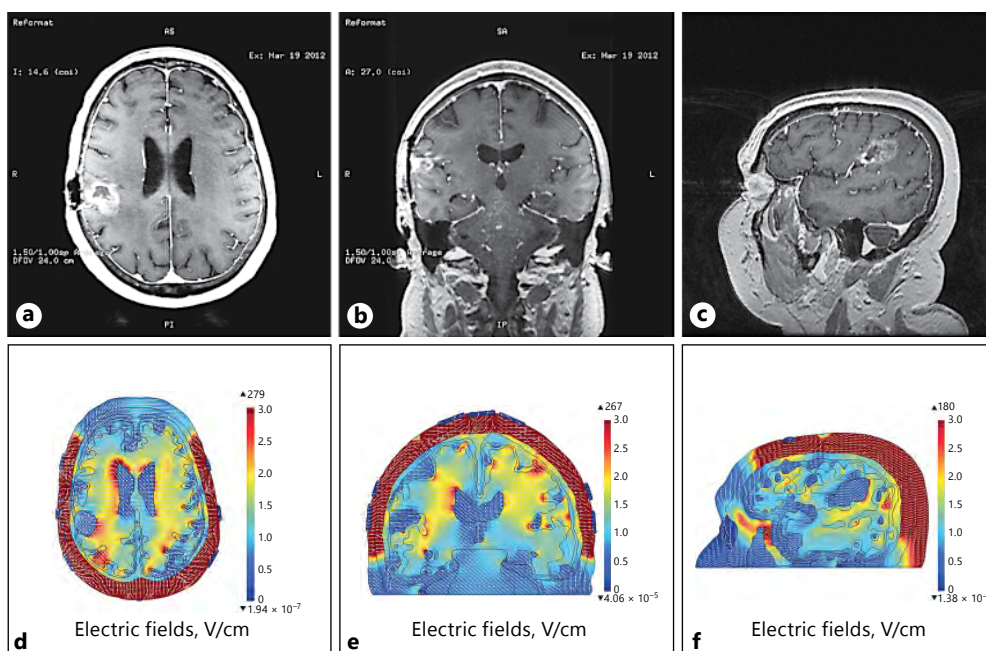




**Fig. 3.** The NovoTTF-100A device consisting of two pairs of orthogonally positioned transducer arrays fixed on the patient's head (courtesy of Aram Boghosian from The Boston Globe).

In concordance with Miranda et al. [43], who used a similar modeling, our group demonstrated inhomogeneous distribution of the induced electric fields throughout the brain [44]. Additionally it was shown that electric fields of higher intensity ( $>3$  V/cm) are located at the interfaces between the cerebrospinal fluid (CSF)-filled spaces (especially, horns of the lateral ventricles) and surrounding tissues [44]. This inhomogeneous distribution may be caused by three possible factors. First, by the relatively large differences in dielectric properties with greater current density in the CSF because fluid is highly conductive. Second, by the differences in the capacitive reactance that oppose changes in electric potential due to the distinct relative permittivity values. Of note, at a constant frequency, the capacitive reactance is inversely proportional to the relative permittivity of tissues. Tissues with lower relative permittivity values exhibit reduced charge retention and thus encounter a lower electric field strength, whereas tissues with higher relative permittivity values may retain larger amounts of charge and will be subjected to a higher electric field intensity. A third factor that may also play a role in the inhomogeneous distribution of TTFields is the specific geometry of the brain, which partially affects the inverse square relationship of the electric field distribution according to Gauss's law. For example, the radial distance between particular sulci and adjacent CSF-filled spaces may vary in different parts of the brain. Nevertheless, further analysis and modeling of TTFields for the treatment of intracranial tumors is definitely needed.





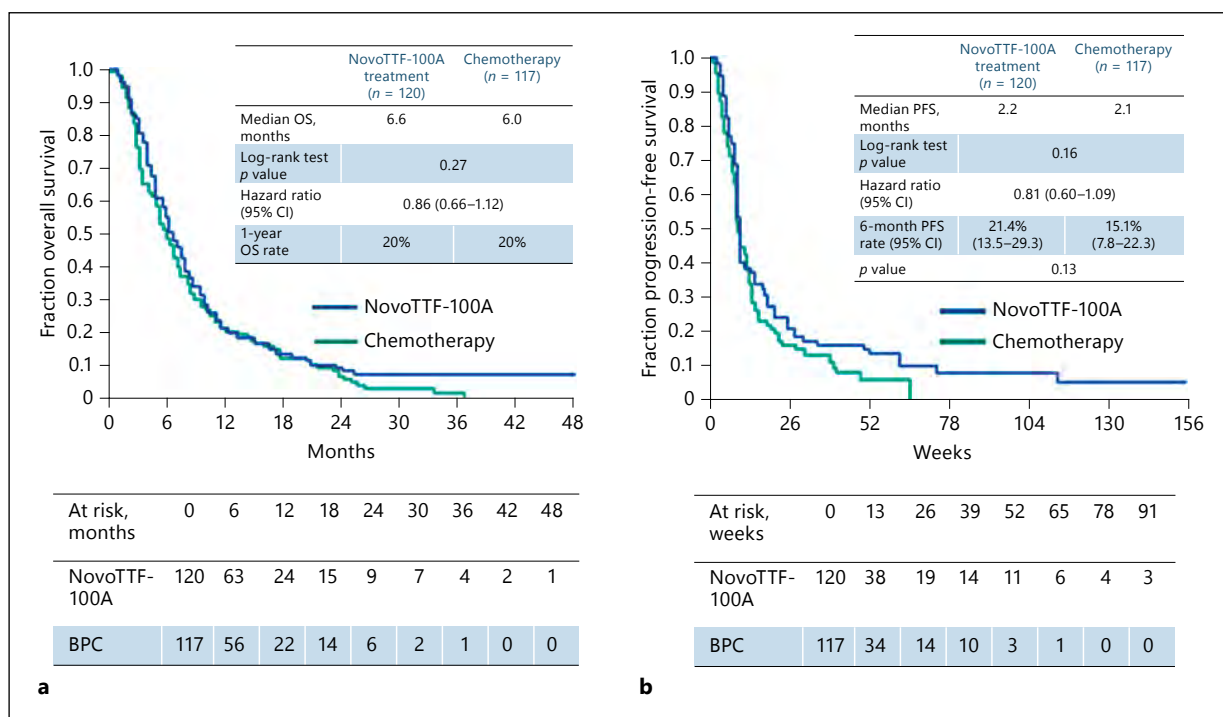
**Fig. 4.** Computer modeling of electric field distribution within the head. Post-contrast T1-weighted MRI in axial (a), coronal (b) and sagittal (c) planes demonstrates recurrent glioblastoma. The electric field distribution was assessed using co-registered post-contrast T1-weighted and T2-weighted images with segmentation of the different intracranial tissues, followed by analysis using finite element modeling software. The final solution is displayed on 2-dimensional plots of the brain in axial (d), coronal (e) and sagittal (f) planes.

### Clinical Results of TTFields Therapy of Intracranial Gliomas

Clinical safety and feasibility of TTFields therapy was initially demonstrated in 10 patients with brain tumors, in one of whom the intracranial electric fields were measured during craniotomy [5]. The median time-to-progression (TTP) of 16.1 weeks (range 3.0–124.0 weeks), overall survival of 62.2 weeks (range 20.3–124.0 weeks), and 1-year survival rate of 67.5% were all favorable in comparison to historical controls [5, 45].

In the pivotal EF-11 phase III study (Table 1) TTFields therapy in patients with recurrent glioblastoma multiforme (GBM) was shown to have comparable efficacy, when compared to the best physician's choice chemotherapy (BPC) that also included bevacizumab (BEV) [8]. There was no obvious hematological and gastrointestinal toxicities. The primary endpoint of this trial was overall survival, which was 6.6 and 6.0 months in patients treated with NovoTTF-100A ( $n = 120$ ) and BPC chemotherapy ( $n = 117$ ), respectively (hazard ratio [HR] 0.86; 95% CI 0.66–1.12;  $p = 0.27$ ). The 1-year survival rate was 20% in both cohorts (Fig. 5). Respective median progression-free survival (PFS) was 2.2 and 2.1 months (HR 0.81; 95% CI 0.60–1.09;  $p = 0.16$ ),





**Fig. 5.** Comparative overall survival (OS [a]) and progression-free survival (PFS [b]) analysis of patients with recurrent glioblastoma according to the prospective randomized EF-11 study demonstrated comparable outcome after TTFields therapy (NovoTTF-100A treatment) and best physician's choice chemotherapy (BPC). From Stupp et al. [8].

whereas 6-month PFS rates were 21.4% (95% CI 13.5–29.3%) and 15.1% (95% CI 7.8–22.3%;  $p = 0.13$ ) [8]. The most common toxicity associated with TTFields therapy was scalp irritation, which was encountered in 14% of patients, but never exceeded grade 2. It could be managed with topical corticosteroids and a slight shift of the arrays during their exchange [46]. The most important advantages associated with the NovoTTF-100A device in comparison to BPC were far fewer instances of grade 2 or greater hematological toxicities (3 vs. 17%) and adverse gastrointestinal events (4 vs. 17%). Quality of life (QOL) analysis demonstrated that patients treated with TTFields therapy had better cognitive and emotional functions than those who received BPC, whereas appetite loss, constipation, diarrhea, fatigue, nausea, vomiting and pain were more often seen in the latter cohort [8]. Based on the comparable efficacy and a lack of serious toxicities, NovoTTF-100A was approved on April 15, 2011 by the FDA for treatment of patients with recurrent GBM.

Clinical characteristics of responders and non-responders to TTFields therapy in the EF-11 cohort were assessed by post hoc analyses [9, 47, 48]. Two characteristics stood out: responders had a higher rate of secondary GBM ( $p = 0.05$ ) and significantly lower dexamethasone usage ( $p < 0.01$ ). Since dexamethasone may cause



**Table 1.** Comparative results of TTFields treatment in patients with recurrent glioblastoma according to the prospective randomized EF-11 study

Evaluated parameters	TTFields treatment (n = 120)	Active chemotherapy (n = 117)	Statistics		
			HR	95% CI	p value
Overall survival [8]			0.86	0.66–1.12	0.27
Median, months	6.6	6.0			
Rates at					
1 year, %	20	20			
2 years, %	8	4			
3 years, %	5	1			
Progression-free survival [8]			0.81	0.60–1.09	0.13
Median, months	2.2	2.1			
Rate at 6 months, %	21	15			
Median overall survival with regard to prognostic factors, months (cases, n) [47]					
Prior bevacizumab failure	6.0 (23)	3.3 (21)	0.43	0.22–0.85	0.02
Prior diagnosis of low-grade glioma	25.3 (12)	7.7 (9)	0.31	0.09–0.99	0.05
Tumor size $\geq 18 \text{ cm}^3$	5.6 (39)	3.3 (41)	0.53	0.32–0.85	<0.01
KPS score $\geq 80$	7.9 (83)	6.1 (77)	0.71	0.51–0.99	0.05
TTFields treatment vs. therapy with bevacizumab	6.6 (120)	4.9 (36)	0.64	0.41–0.99	0.05
Median overall survival with regard to tumor response, months, (cases, n) [48]					
Partial and complete response	24.7 (14)		1.0		
Stable disease	7.6 (34)		0.28	0.14–0.58	<0.01
Progressive disease	5.5 (59)		0.24	0.14–0.42	<0.01
Prognostic factor in responders to TTFields treatment [9]					
Median survival with regard to prior diagnosis of low-grade glioma (yes/no), months	27.7 vs. 16.6				0.05
Median dexamethasone dose, mg [9]					
Daily (responders/non-responders)	1.0/5.2				<0.01
Cumulative (responders/non-responders)	7.1/261.7				<0.01
Incidence of treatment-related adverse events $\geq$ grade 2, % [8, 46]					
Hematological	3	17			
Gastrointestinal	4	17			
Dermatological	2	0			
Nervous system disorders	30	28			

KPS, Karnofsky performance scale; TTFields, tumor treating fields; HR, hazard ratio.

immunosuppression in cases of GBM undergoing standard FRT and concomitant TMZ [49], the same effect is most likely imposed onto NovoTTF-100A-treated patients and affects their anticancer immunity [9].

The efficacy of TTFields therapy in clinical practice was analyzed using the Patient Registry Dataset (PRiDe), which included 457 cases of recurrent GBM treated with



**Table 2.** Results of TTFields treatment in patients with recurrent glioblastoma ( $n = 457$ ) according to the Patient Registry Dataset [50]

Evaluated parameters	Results	Statistics		
		HR	95% CI	<i>p</i> value
Overall survival				
Rates at				
1 year, %	44			
2 years, %	30			
Median overall survival with regard to number of prior recurrences, months				
First recurrence	20	1.0		
Second recurrence	8.5	0.6	0.4–0.9	0.03
Third-to-fifth recurrence	4.9	0.3	0.2–0.5	<0.01
Median overall survival with regard to patient daily compliance to treatment, months				
<75%	4.0	1.0		
≥75%	13.5	0.4	0.3–0.6	<0.01
Median overall survival with regard to prior therapy with bevacizumab, months				
No	13.4	1.0		
Yes	7.2	0.5	0.4–0.7	<0.01
Median overall survival with regard to KPS score, months				
90–100	14.8	1.0		
70–90	7.7	0.6	0.4–0.9	<0.01
10–60	6.1	0.4	0.2–0.6	<0.01
Median overall survival with regard to prior debulking surgery, months				
No	8.9	1.0		
Yes	9.8	1.1	0.8–1.5	0.79

KPS, Karnofsky performance scale; HR, hazard ratio.

NovoTTF-100A across 91 medical centers in the USA [50]. In comparison to the results of the EF-11 trial, more patients in PRiDe received treatment at the time of first tumor recurrence (9 vs. 33%). Median overall survival (9.6 vs. 6.6 months), as well as 1-year (44 vs. 20%), and 2-year (30 vs. 9%) survival rates were greater in PRiDe in comparison to the EF-11 cohort. Initiation of TTFields therapy at the time of first or second recurrence (as compared to third, fourth, or fifth recurrence) and no prior BEV administration were significantly ( $p < 0.01$ ) associated with longer survival (Table 2) [50]. These data further support the benefits of TTFields therapy in cases of recurrent GBM with regard to treatment tolerability, safety, and potential efficacy.

A multicenter EF-14 trial randomized 695 enrolled patients (of preplanned 700) with newly diagnosed GBM after completion of standard FRT concomitant with daily



**Table 3.** Results of TTFields treatment in patients with newly diagnosed glioblastoma according to interim analysis of the prospective randomized EF-14 study [10]

Evaluated parameters	TTFields treatment plus temozolomide ( <i>n</i> = 210)	Temozolomide alone ( <i>n</i> = 105)	Statistics	
			HR	<i>p</i> value
Median overall survival, months	19.6	16.6	0.75	0.034
Median progression-free survival, months	7.1	4.0	0.6	0.001

TTFields, tumor treating fields; HR, hazard ratio.

TMZ in a 2:1 ratio for either adjuvant TTFields therapy combined with TMZ or for adjuvant TMZ alone [51]. The primary endpoint of this study was PFS, and the secondary endpoints were overall survival, 1- and 2-year survival rates, 6-month PFS rate, radiological response, and QOL parameters. In a prespecified interim analysis of the first 315 cases after a minimum follow-up of 18 months (Table 3), the intention-to-treat (ITT) cohort, which received adjuvant TTFields therapy combined with TMZ (*n* = 210) had longer PFS in comparison to those treated with adjuvant TMZ alone (*n* = 105); the median PFS was 7.1 months (95% CI 5.9–8.2 months) vs. 4.0 months (95% CI 3.0–4.3 months), respectively (HR 0.6; *p* = 0.0014) [10]. The overall survival was also longer with adjuvant TTFields therapy combined with TMZ (median survival 19.6 months; 95% CI 16.5–24.1 months vs. 16.6 months; 95% CI 13.5–19.1 months; HR 0.75; *p* = 0.034). The same trend was revealed in the protocol population that started the second cycle of treatment (median survival 20.5 months; 95% CI 16.5–24.1 months; *n* = 196 vs. 15.5 months; 95% CI 13.5–19.1 months; *n* = 84; HR 0.67, *p* = 0.0072). There were no unexpected adverse events, whereas grades 3–4 hematological toxicities (12 vs. 9%), gastrointestinal disorders (5 vs. 2%), and seizures (7 vs. 7%) were similar between the two treatment cohorts. Scalp reactions were more common in patients treated with TTFields (49 vs. 5% for grade 1–2, and 7 vs. 5% for grade 3–4 toxicities) [10]. Thus, preliminary data from the EF-14 study indicate that adjuvant treatment with Novo-TTF-100A combined with TMZ may offer survival advantage in patients with newly diagnosed GBM. A recent 5-year survival analysis of all 695 patients of this trial also showed a sustained benefit of such therapy.

## Conclusion

The evolution of TTFields therapy from the initial laboratory observations of cell membrane blebbing during mitosis to *bona fide* treatment of patients with GBM is an excellent testament to the value of translational neuro-oncology research. Our understanding of the physical attributes, cellular biology effects, and clinical efficacy of TTFields have improved dramatically. Widespread application of this therapeutic



modality in the future will require optimization of treatment regimens by combining TTFields therapy with conventional chemotherapy, FRT, stereotactic radiosurgery, molecular targeted therapy, and/or immunotherapy.

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## Policy

Aetna considers devices to generate electric tumor treatment fields (ETTF) medically necessary as monotherapy for persons with histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma), after histologically or radiologically confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy.

Aetna considers combination of devices to generate ETTF and temozolomide medically necessary as adjunctive treatment of newly-diagnosed histologically confirmed supratentorial glioblastoma following standard treatments that include surgery, chemotherapy, and radiation therapy.

Aetna considers devices to generate ETTF experimental and investigational for the treatment of other malignant tumors (e.g., breast, lung, melanoma, ovarian cancer, pancreatic cancer, and solid tumor brain metastases; not an all-inclusive list) and for all other indications because their effectiveness has not been established.

Aetna considers combined ETTF therapy and chemo-immuno-therapy other than temozolomide (e.g., 6-thioguanine, bevacizumab, capecitabine, celecoxib, cisplatin, cyclophosphamide, dacarbazine, doxorubicin, lomustine, paclitaxel, and pemetrexed; not an all-inclusive list) for the treatment of other malignant tumors experimental and investigational because the effectiveness of this approach has not been established.

## Background

Alternating electric fields, generated by insulated electrodes, have been reported to exhibit inhibitory effect on the growth rate of a variety of human and rodent tumor cell lines as well as malignant tumors in animals. This non-thermal effect selectively affects dividing cells while quiescent cells are left intact. There are 2 modes of action for these anti-tumoric effects:

- I. arrest of cell proliferation, and
- II. destruction of cells while undergoing division.
  
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- II. destruction of cells while undergoing division.

Both effects were observed when such fields were applied for 24 hours to cells undergoing mitosis that is oriented along the field direction. The 1st mode of action is manifested by interference with the proper formation of the mitotic spindle, while the 2nd mode of action results in rapid disintegration of the dividing cells. Both effects are consistent with the computed directional forces exerted by these specific fields on charges and dipoles within the dividing



cells. In-vivo treatment of tumors in C57BL/6 and BALB/c mice resulted in significant slowing of tumor growth and extensive destruction of tumor cells within 3 to 6 days. These findings showed the potential applicability of alternating electric fields as a novel therapeutic modality for malignant tumors (Kirson et al, 2004).

Electric tumor treating fields (ETTF), also known as alternating electrical field therapy, are low-intensity (1 to 2 V/cm), intermediate-frequency (100 to 200 kHz), alternating electric fields employed for the treatment of malignant tumors. ETTFs are delivered to a malignant tumor site via insulated electrodes placed around the region of the body containing the tumor. This novel treatment modality has shown promise in pilot clinical trials in patients with advanced stage solid tumors including glioblastoma (GBM).

Kirson et al (2007) reported the findings of a pilot clinical trial examining the effects of ETTF in 10 patients with recurrent GBM. Median time to progression (TTP) in these patients was 26.1 weeks and median overall survival (OS) was 62.2 weeks. The authors noted that these TTP and OS values were more than double the reported medians of historical control patients. No device-related serious adverse events (AEs) were seen after more than 70 months of cumulative treatment in all of the patients. The only device-related AE observed was a mild-to-moderate contact dermatitis beneath the field delivering electrodes. The authors concluded that ETTF are a safe and effective new treatment modality that effectively slows down tumor growth in-vitro, in-vivo, as well as in human cancer patients.

In a pilot study, Salzberg and colleagues (2008) evaluated the safety, tolerability, and effectiveness of ETTF treatment in patients with locally advanced or metastatic solid tumors using the NovoTTF-100A device. A total of 6 patients were heavily pre-treated with several lines of therapy; no additional standard treatment option was available to them. Electric tumor treating fields treatment using continuous NovoTTF-100A lasted a minimum of 14 days and was well-tolerated. No related serious AEs occurred. Outcomes showed 1 partial response of a treated skin metastasis from a primary breast cancer, 3 cases where tumor growth was arrested during treatment, and 1 case of disease progression. One mesothelioma patient experienced lesion regression near ETTF with simultaneous tumor stability or progression in distal areas. The authors concluded that although the number of patients in this study was small, the lack of therapy toxicity and the effectiveness observed in data gathered to date indicate the potential of ETTF as a new treatment modality for solid tumors, thus, warranting further investigation.

Recent reviews indicated the ETTF is a promising approach for the treatment of GBM and non-small cell lung cancer. Stupp and Weller (2010) noted that novel treatment approaches in recurrent GBM include anti-angiogenic agents (e.g., bevacizumab and cilengitide) as well as ETTF (NovoTTF). Furthermore, Pless and Weinberg (2011) reviewed in-vitro and in-vivo pre-clinical studies, showing the activity of ETTF both as a monotherapy as well as in combination with several cytotoxic agents. They also summarized the clinical experience with ETTF, mainly in 2 indications:

- I. recurrent GBM: in a prospective randomized phase III trial, ETTF was compared with best standard care (BSC, including chemotherapy): ETTF significantly improved median OS



compared with standard therapy (7.8 versus 6.1 months) for the patients treated per protocol (Stupp et al, 2010; published as an abstract). Importantly, quality-of-life was also better in the ETTF group (Ram et al, 2010);

- II. a phase II study of second-line treatment of non-small cell lung cancer, where ETTF was administered concomitantly with pemetrexed.
- I. recurrent GBM: in a prospective randomized phase III trial, ETTF was compared with best standard care (BSC, including chemotherapy): ETTF significantly improved median OS compared with standard therapy (7.8 versus 6.1 months) for the patients treated per protocol (Stupp et al, 2010; published as an abstract). Importantly, quality-of-life was also better in the ETTF group (Ram et al, 2010);
- II. a phase II study of second-line treatment of non-small cell lung cancer, where ETTF was administered concomitantly with pemetrexed.

This combination resulted in an excellent median OS of 13.8 months (Pless et al, 2010; published as an abstract). Interestingly, the progression-free survival (PFS) within the area of the ETTF was 28 weeks; however, outside the ETTF the PFS was only 22 weeks. This is an important finding because it can be assumed that in the same patient the higher tumor control within the tumor-treating fields (TTFields) area was a specific effect of TTFields. Median OS was 13.8 months and 1-year survival was 57 %; 6 patients (14.6 %) had a radiological partial remission and 16 patients had stable disease (39 %). The authors stated that these results are promising and compare well with matched historical controls treated with pemetrexed alone in second-line treatment. The authors stated that the proof of concept of ETTF has been demonstrated in the pre-clinical setting, and the clinical data seem promising in various tumor types. The side effects of ETTF were minimal and in general consisted of skin reaction to the electrodes. The authors said that there are a number of ways in which ETTF could be further evaluated, for example, in combination with chemotherapy, as a maintenance treatment, or as a salvage therapy if radiotherapy or surgery is not possible. The authors concluded that while more clinical data are clearly needed, ETTF is an emerging and promising novel treatment concept (Pless and Weinberg, 2011).

On April 15, 2011, the Food and Drug Administration (FDA) approved the NovoTTF-100A System (Novocure, Portsmouth, NH) for the treatment of adults with GBM that recurs or progresses after receiving chemotherapy and radiation therapy. The NovoTTF-100A System is not intended to be used in combination with other cancer treatments. It should only be used after other treatments have failed. The FDA-approved indication for use is: "The NovoTTF-100A System is intended as treatment for adult patients (22 years of age or older) with histologically confirmed glioblastoma multiforme (GBM), following histologically or radiologically confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted."

The approval was based on data presented to the FDA from a multi-national, randomized, controlled study. The expedited pre-market approval (PMA) includes a requirement for a post-market non-randomized, unblinded, concurrent control study of NovoTTF-100A in patients with recurrent GBM. The primary question to be addressed by the study (FDA, 2011): "Is the overall



survival of patients treated with NovoTTF-100A non-inferior to the survival of patients treated with the best standard of care (chemotherapy)"?

The first randomized clinical study of ETTF did not reach its primary end-point of improved survival compared to active chemotherapy (Stupp et al, 2012; Novocure, 2012). This study was funded and sponsored by the device manufacturer, Novocure, Ltd. Subjects for this study were age 18 years or older with histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma) with radiologically confirmed disease progression. Patients had a Karnofsky performance status greater than or equal to 70 %, and adequate hematologic, renal and hepatic function (absolute neutrophil count greater than or equal to 1,000/mm<sup>3</sup>, hemoglobin greater than or equal to 100 g/L, platelet count greater than or equal to 100,000/mm<sup>3</sup>, serum creatinine level less than or equal to 1.7 mg/dL, total serum bilirubin less than or equal to the upper limit of normal, and liver function values less than 3 times the upper limit of normal. Prior therapy must have included radiotherapy (with and without concomitant and/or adjuvant temozolomide). Patients with infra-tentorial tumor location were excluded, as were patients with implanted electronic medical devices (e.g. pacemaker, programmable ventriculo-peritoneal shunt). Patients were randomized in a 1:1 ratio to receive either NovoTTF-100A without chemotherapy or the physician's choice of active chemotherapy (active control). Chemotherapy agents considered as best standard of care (BSC) during the study included platinum-based chemotherapy (i.e., carboplatin); nitrosureas; procarbazine; combination of procarbazine, lomustine and vincristine; temozolomide; and bevacizumab. For patients assigned to Novo-TTF, uninterrupted treatment was recommended, although patients were allowed to take treatment breaks of up to 1 hour, twice per day, for personal needs (e.g., shower). In addition, patients assigned to Novo-TTF were allowed to take 2 to 3 days off treatment at the end of each of 4 week (which is the minimal required treatment duration for TTF therapy to reverse tumor growth). A period of 28 days of treatment with ETTF was considered 1 full treatment course. The primary end-point of the study was OS. Secondary end-points included PFS rates at 6-months; median time to progression (TTP), 1-year survival rate; quality-of-life; and radiological response. Subjects were seen in clinic monthly, and magnetic resonance imaging (MRI) was performed after 2, 4 and 6 months from initiation of treatment and subsequent MRIs were done according to local practice until disease progression. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with the subjects' caregivers were used to evaluate subject mortality rates. A total of 28 clinical centers enrolled 237 adult subjects with 120 subjects randomized to the NovoTTF treatment group and 117 subjects randomized to the BSC group. A total of 30 subjects never started on trial (4 in the treatment group and 26 in the BSC group); 207 subjects started on trial, with 79 % discontinuation rate (n = 47 deaths; n = 49 deterioration of condition; and n = 68 study requirements of 2 additional clinic visits after disease progression were completed). Consent was withdrawn before completing 2 months of post-progression follow-up in 20 subjects. Adverse events led to 20 additional subject withdrawals. Non-compliance with follow-up was attributed to 3 subjects. The proportions were similar between the NovoTTF-100A group and the BSC group of subjects who did not complete the protocol-defined follow-up due to withdrawal of consent, non-compliance, or AEs. An average of 4.2 months of TTF treatment per subject was completed for the 116 subjects in the active treatment cohort. Complete vital statistics were known for 93 % (221 subjects) at the end of the study. There were 202 known deaths and 19 subjects (ETTF =



9; BSC = 10) were still alive 6 months after the last subject was randomized; 16 (7 %) subjects were lost to follow-up.

The trial did not reach its primary end-point of improved survival compared to active chemotherapy (Stupp et al, 2011; Novocure, 2012). In addition, differences in response rates, PFS at 6 months, and reduction in risk of death were not statistically significant. Quality of life analyses favored ETTF therapy in most domains. The differences in median OS between patients in the NovoTTF-100A group and the BSC group were not statistically significant. According to the FDA, the median OS is 6.3 months (95 % confidence interval [CI]: 5.6 to 7.8) in the NovoTTF-100A group and 6.4 months (95 % CI: 5.2 to 7.4) in the BSC group (log rank  $p = 0.98$ ; Wilcoxon  $p = 0.72$ ). The hazard ratio (HR) is 1.0 (95 % CI: 0.76 to 1.32) (test for proportional hazards  $p = 0.45$ ). In the active chemotherapy control arm of the trial, survival was not significantly affected by the choice of chemotherapy. The Kaplan-Meier survival curve for the 2 treatment groups appeared to be very similar during the first 12 months of follow-up. Between 12 and 24 months, the survival curves separated slightly in favor of the BSC control group. There were no statistically significant differences in secondary end-points of 1-year survival, PFS, radiologic response rates, and median TTP. Mild-to-moderate (grade 1 and 2) contact dermatitis on the scalp beneath the transducer arrays occurred in 16 % of ETTF patients. Patients receiving active control chemotherapy experienced toxicity related to pharmacologic mechanism of the agents used: gastrointestinal (30 % versus 8 %), hematological (19 % versus 4 %) and infectious (12 % versus 4 %). Longitudinal Quality of Life (QOL) was available in only 27 % of subjects (63 patients) who remained on study therapy for 3 months and for whom QOL data were available. In the domains of global health and social functioning, no meaningful differences between chemotherapy and ETTF were observed. However, cognitive, emotional, and role functioning favored ETTF, whereas physical functioning favored chemotherapy. Symptom scale analysis is in accordance to treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the ETTF treatment group.

Commenting on the trial by Stupp et al, Debonis et al (2012) stated that the study was designed for superiority; although well conducted, it might not have shown it for a limited compliance in the ETTF group. Debonis et al (2012) stated that, even with this limitation, the trial by Stupp et al has shown at least equivalence of ETTF to chemotherapy, with a decreased toxicity and increased quality of life favoring ETTF.

The manufacturer initiated a subsequent randomized clinical trial enrolling newly diagnosed glioblastoma patients after completion of standard radiochemotherapy, parallel to starting the adjuvant or maintenance temozolomide chemotherapy (Stupp et al, 2012). Patients randomized to the experimental arm received ETTF in addition to maintenance temozolomide. In an abstract, Stupp et al (2014) reported on an interim analysis of this international, multi-center, prospective, randomized phase III trial in newly diagnosed GBM patients. After completion of radiotherapy (RT) with concomitant temozolomide (TMZ), patients were randomized (2:1) to adjuvant TMZ with NovoTTF or adjuvant TMZ alone. The primary end-point was PFS, with OS an important secondary end-point. Analysis was by intention-to-treat. The investigators reported on a pre-specified interim analysis of the first 315 patients randomized, after a



minimum follow-up of 18 months (range of 18 to 60 months). Investigators randomized 210 patients NovoTTF/TMZ and 105 to TMZ alone. Patient characteristics were balanced: median age of 57 and 58 years, tumor resection in 89 and 90 %, KPS 90 %, for the NovoTTF and the control arms, respectively. MGMT promoter methylation status was assessable centrally in 60 % of patients; of these 39 % and 41 % were methylated. Adverse events (AE) were comparable between treatment arms. The most common device-related AE was skin irritation in 45 % of patients (all grades, severe 2 %). Severe seizures were observed at a frequency of 7 % in both arms. Median PFS was 7.1 months [mo] (95 % CI: 5.9 to 8.2) and 4.0 mo (CI: 3.0 to 4.3; HR 0.63,  $p = 0.001$ ), OS was 19.6 mo (CI: 16.5 to 24.1) and 16.6 mo (CI: 13.5 to 19.1) (HR 0.75,  $p = 0.034$ ), both favoring NovoTTF. This translated into a 24-mo survival rate of 43 % (CI: 36 to 50 %) and 29 % (CI: 21 to 39 %) for the NovoTTF/TMZ and the TMZ alone arm, respectively. The investigators stated that the trial met its primary and main secondary end-points, and was closed to accrual after this interim analysis. The investigators concluded that adjuvant TMZ chemotherapy and NovoTTF provided a clinically and statistically significant improvement in PFS and OS, and should become the new standard of care against GBM.

The National Comprehensive Cancer Network (NCCN, 2013) had a Category 2B recommendation to consider the use of ETTF for persons with local, diffuse or multiple recurrences of glioblastoma. This was changed to a Category 3 recommendation in 2014 (NCCN, 2014). NCCN guidelines explain that approval of tumor treating fields (TTF) for recurrent glioblastoma was based on results of a clinical trial that randomized 237 patients to TTF or chemotherapy. Similar survival was observed in the 2 arms, and TTF therapy was associated with lower toxicity and improved quality of life. Due to the lack of efficacy, not all NCCN panelists recommended the treatment. This was subsequently changed to a category 2B recommendation in 2015 (NCCN, 2015).

Medicare Durable Medical Equipment Medicare Administrative Contractor (DME MAC) considers tumor treatment field therapy not reasonable and necessary for Medicare beneficiaries (NHIC, 2014).

On October 5, 2015, the FDA approved an expanded indication for the Optune device (using alternating electrical fields called “tumor treatment fields” [TTFields]) to treat patients with newly-diagnosed GBM. It is administered along with temozolomide (TMZ) following standard treatments that include surgery, chemotherapy, and radiation therapy. In the clinical study used to support the expanded indication, patients treated with the device and TMZ lived on average 3 months longer than those treated with the drug alone. Optune was initially approved in 2011 to treat patients with GBM that recurred or progressed after chemotherapy. With this expanded indication, Optune can be used as part of a standard treatment for GBM before the disease progresses. For newly diagnosed GBM, Optune is not intended to be used as a substitute for standard treatments, but rather as an adjunct therapy. The device is portable and can be powered with batteries or plugged into an electrical outlet. Patients can use the device at home or work, allowing them to continue their normal daily activities.

The FDA based its approval of the expanded indication of the Optune device on results from a clinical trial involving 695 patients newly diagnosed with GBM that compared those who used



Optune with TMZ to those receiving TMZ alone. Patients who used the device along with TMZ lived, on average, about 7 months with no disease progression compared to 4 months for those who had the drug alone. The Optune plus TMZ group survived for an average of 19.4 months after diagnosis compared to 16.6 months for those who were treated with only TMZ. The most common side effect experienced with Optune was skin irritation. Clinical trial participants also experienced a slightly higher incidence of neurological side effects, including convulsions and headaches, compared to subjects receiving TMZ alone. Patients should not use the Optune system if they have an active implanted medical device or a skull defect, have an underlying skin condition involving the scalp or have a known sensitivity to conductive hydrogels, such as those used on electrocardiogram stickers.

Electric tumor treating fields technology is also being studied as a treatment for other solid tumors (e.g., melanoma and non-small cell lung cancer). However, there is a paucity of published evidence from randomized controlled trials examining the long-term safety and effectiveness of ETTF as a treatment of tumors.

Davis et al (2013) stated that TTFields therapy has been demonstrated in multiple cell lines when the appropriate frequency was utilized. A phase III trial of TTFields monotherapy compared to active chemotherapy in recurrent glioblastoma patients established that TTFields therapy is associated with minimal toxicity, better quality of life, and comparable efficacy to chemotherapy. Ongoing and future trials will evaluate TTFields in newly diagnosed glioblastoma, solid tumor brain metastases, non-small cell lung cancer, and ovarian and pancreatic cancers.

The NovoTAL System is a workstation-based software tool that uses MRI head morphology, tumor size and location measurements, and tissue di-electric properties to optimize TTFields distribution and intensity within the brain tumor. This system is part of the NovoTTF electronic tumor treatment fields treatments used for the treatment of GBM.

## **Melanoma:**

Li and colleagues (2016) proposed a method of using electrical stimulation for treatment of malignant melanoma through directly spray-printing liquid metal on skin as soft electrodes to deliver low intensity, intermediate frequency electric fields. With patterned conductive liquid metal components on mice skin and under assistance of a signal generator, a sine wave electrical power with voltage of 5 V and 300 kHz could be administrated on treating malignant melanoma tumor. The experiments demonstrated that tumor volume was significantly reduced compared with that of the control group. Under the designed parameters (signal: sine wave, signal amplitude  $V_{pp}$ : 5 V and  $V_{pp}$ : 4 V, frequency: 300 kHz) of Tumor treating fields (TTFields) with the sprayed liquid metal electrode, 4 mice tumor groups became diminishing after 1 week of treatment. The only device-related side effect as seen was a mild-to-moderate contact dermatitis underneath the field delivering electrodes. The scanning electron microscope (SEM) images and pathological analysis demonstrated the targeted treating behavior of the malignant melanoma tumor. Further, thermal infrared imaging experiments indicated that there was no evidence of heating effects in the course of treatment. Besides, the liquid metal was easy to remove through



medical alcohol. The authors concluded that tumor treating fields through liquid metal electrode could offer a safe, straightforward and effective treatment modality that slowed down tumor growth *i- vivo*. They stated that these promising results also raised the possibility of applying spray-printing TTFields as an easy going physical way for future cancer therapy.

### **Combination of ETTF and Chemo-Immuno-Therapy for Other Malignant Tumors:**

In a pilot, in-vitro and in-vivo, clinical trial, Kirson et al (2009) examined the effectiveness and toxicity of combining TTFields with chemotherapeutic treatment. Cell proliferation in culture was studied in human breast carcinoma (MDA-MB-231) and human glioma (U-118) cell lines, exposed to TTFields, paclitaxel, doxorubicin, cyclophosphamide and dacarbazine (DTIC) separately and in combinations. In addition, these researchers studied the effects of combining chemotherapy with TTFields in an animal tumor model and in a pilot clinical trial in recurrent and newly diagnosed GBM patients. The effectiveness of TTFields-chemotherapy combination in-vitro was found to be additive with a tendency towards synergism for all drugs and cell lines tested (combination index less than or equal to 1). The sensitivity to chemotherapeutic treatment was increased by 1 to 3 orders of magnitude by adjuvant TTFields therapy (dose reduction indexes 23 to 1,316). Similar findings were seen in an animal tumor model. Finally, 20 GBM patients were treated with TTFields for a median duration of 1 year. No TTFields-related systemic toxicity was observed in any of these patients, nor was an increase in temozolomide toxicity seen in patients receiving combined treatment. In newly diagnosed GBM patients, combining TTFields with temozolomide treatment led to a PFS of 155 weeks and OS of 39+ months. The authors concluded that these results indicated that combining chemotherapeutic cancer treatment with TTFields may increase chemotherapeutic effectiveness and sensitivity without increasing treatment related toxicity.

Pless et al (2013) noted that TTFields exhibit anti-mitotic activity in cancer cells, and promising pre-clinical data have led to a single-arm phase I/II clinical trial in patients with non-small cell lung cancer (NSCLC). A total of 42 inoperable stage IIIB (with pleural effusion) and stage IV NSCLC patients who had had tumor progression received intravenous pemetrexed 500 mg/m<sup>2</sup> q3w together with daily TTFields therapy until disease progression. The primary end-point was time to "in-field" progression. Median age for all patients was 63 years, 76 % had stage IV disease, 78 % had adenocarcinoma and 17 % had performance status of 2. The median time to in-field progression was 28 weeks and the median time to systemic progression was 22 weeks. Six patients (14.6 %) had a partial remission (PR) and 20 had stable disease (SD) (48.8 %). Median OS was 13.8 months and 1 year survival rate was 57 %. There were no TTFields-related serious adverse events. The authors concluded that the combination of TTFields and pemetrexed as a second-line therapy for NSCLC is safe and potentially more effective than pemetrexed alone. They stated that TTFields improved disease control within the treatment field and a phase III study is planned to further investigate its role as a novel treatment in NSCLC.

Giladi et al (2014) stated that NSCLC is one of the leading causes of cancer-related deaths worldwide. Common treatment modalities for NSCLC include surgery, radiotherapy, chemotherapy, and, in recent years, the clinical management paradigm has evolved with the advent of targeted therapies. Despite such advances, the impact of systemic therapies for



advanced disease remains modest, and as such, the prognosis for patients with NSCLC remains poor. Standard modalities are not without their respective toxicities and there is a clear need to improve both safety and effectiveness for current management approaches. Tumor-treating fields are low-intensity, intermediate-frequency alternating electric fields that disrupt proper spindle microtubule arrangement, thereby leading to mitotic arrest and ultimately to cell death. These researchers evaluated the effects of combining TTFields with standard chemotherapeutic agents on several NSCLC cell lines, both in-vitro and in-vivo. Frequency titration curves demonstrated that the inhibitory effects of TTFields were maximal at 150 kHz for all NSCLC cell lines tested, and that the addition of TTFields to chemotherapy resulted in enhanced treatment efficacy across all cell lines. They investigated the response of Lewis lung carcinoma and KLN205 squamous cell carcinoma in mice treated with TTFields in combination with pemetrexed, cisplatin, or paclitaxel and compared these to the efficacy observed in mice exposed only to the single agents. Combining TTFields with these therapeutic agents enhanced treatment efficacy in comparison with the respective single agents and control groups in all animal models. The authors concluded that these findings suggested that combining TTFields therapy with chemotherapy may provide an additive efficacy benefit in the management of NSCLC. They stated that further prospective studies to examine the optimal combinations of therapy are needed.

Omar (2014) stated that prior to the approval of the TTF System, the only FDA approved treatment for recurrent GBM (rGBM) was bevacizumab. By blocking the VEGF pathway, bevacizumab can result in a significant radiographic response (pseudo-response), improve PFS and reduce corticosteroid requirements in rGBM patients. Bevacizumab however failed to prolong OS in a recent phase III trial. A pivotal phase III trial (EF-11) demonstrated comparable OS between physicians' choice chemotherapy and TTF Therapy but better quality of life were observed in the TTF arm. There is currently an unmet need to develop novel approaches designed to prolong OS and/or improve quality of life in this unfortunate patient population. One appealing approach would be to combine the 2 currently approved treatment modalities namely bevacizumab and TTF Therapy. These 2 treatments are currently approved as monotherapy, but their combination has never been evaluated in a clinical trial.

Wong et al (2015) treated a series of patients with NovoTTF-100A and bevacizumab alone (n = 34) or in combination with a regimen consisting of 6-thioguanine, lomustine, capecitabine, and celecoxib (TCCC) (n = 3). Compared to the former cohort, the latter cohort exhibited a trend for prolonged OS, median of 4.1 (0.3 to 22.7) months versus 10.3 (7.7 to 13.6) months, respectively (p = 0.0951), with 1 experiencing an objective response with a 50 % reduction in tumor size on MRI despite possessing a larger tumor size at baseline and more severe neurologic dysfunction than the median for either group. These preliminary observations illustrated the possibility of improving survival and achieving a response in patients with end-stage recurrent glioblastoma by biasing the tumor toward anti-tumor immunologic response with a combination of NovoTTF-100A and TCCC, as well as the continuation of bevacizumab in order to limit dexamethasone use due to its global immunosuppressive effect on the patient.



**Table: CPT Codes / HCPCS Codes / ICD-10 Codes**

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":*

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Code	Code Description
<b>ICD-hyphen10 codes will become effective as of October 1, 2015:</b>	
<b>HCPCS codes covered if selection criteria are met:</b>	
<b>A4555</b>	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
<b>E0766</b>	Electrical stimulation device used for cancer treatment, includes all accessories, any type
<b>J8700</b>	Temozolomide, oral, 5 mg
<b>J9328</b>	Injection, temozolomide, 1 mg
<b>ICD-hyphen10 codes covered if selection criteria are met:</b>	
<b>C71.0 -hyphen C71.9</b>	Malignant neoplasm of brain [supratentorial glioblastomas (WHO grade IV astrocytomas)]
<b>ICD-hyphen10 codes not covered for indications listed in the CPB (not all inclusive):</b>	
<b>C11.0 -hyphen C11.9</b>	Malignant neoplasm of nasopharynx
<b>C15.3 -hyphen C15.9</b>	Malignant neoplasm of esophagus
<b>C16.0 -hyphen C16.9</b>	Malignant neoplasm of stomach
<b>C18.0 -hyphen C18.9</b>	Malignant neoplasm of colon
<b>C19 -hyphen C21.8</b>	Malignant neoplasm of rectosigmoid junction, rectum, anus and anal canal
<b>C22.1</b>	Intrahepatic bile duct carcinoma
<b>C23 -hyphen C24.9</b>	Malignant neoplasm of gall bladder and other and unspecified parts of biliary tract



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Code	Code Description
<b>C25.0 -hyphen C25.9</b>	Malignant neoplasm of pancreas
<b>C31.0 -hyphen C31.9</b>	Malignant neoplasm of accessory sinuses (paranasal)
<b>C33 -hyphen C34.92</b>	Malignant neoplasm trachea, bronchus, and lung
<b>C37</b>	Malignant neoplasm of thymus
<b>C43.0 -hyphen C43.9</b>	Malignant neoplasm of skin
<b>C46.1</b>	Kaposi's sarcoma of soft tissue
<b>C49.0 -hyphen C49.9</b>	Malignant neoplasm of peripheral nerves, autonomic nervous system and other connective and soft tissue
<b>C50.011 -hyphen C50.929</b>	Malignant neoplasm of breast
<b>C53.0 -hyphen C53.9</b>	Malignant neoplasm of cervix uteri
<b>C54.0 -hyphen C54.9</b>	Malignant neoplasm of corpus uteri
<b>C56.1 -hyphen C56.9</b>	Malignant neoplasm of ovary
<b>C57.00 -hyphen C57.02</b>	Malignant neoplasm of fallopian tube



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*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":*

Code	Code Description
<b>C61</b>	Malignant neoplasm of prostate
C64.1 -hyphen C66.9 C68.0 -hyphen C68.9	Malignant neoplasm of kidney and other and unspecified urinary organs
<b>C73</b>	Malignant neoplasm of thyroid gland
<b>C79.31</b>	Secondary malignant neoplasm of brain [solid tumor brain metastases]
<b>D00.00 -hyphen D09.9</b>	Carcinoma in situ

**The above policy is based on the following references:**

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- [Last Review](#) 12/06/2017 <a href="/cpb/medical/data/disclaimer/review/800\_899/0827\_11.html" target="\_blank">Last Review</a>&nbsp;12/06/2017  
Effective: 03/16/2012  
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## Medical Policy Bulletin

Title: **Tumor Treating Fields**

Policy #: **07.03.26**

The below medical or claim payment policy is applicable to the Company's commercial products only. Policies that are applicable to the Company's Medicare Advantage products are accessible via a separate [Medicare Advantage policy database](#).

The Company makes decisions on coverage based on Policy Bulletins, benefit plan documents, and the member's medical history and condition. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Medical Policy Bulletin document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged or new medical literature may have been published. This Medical Policy Bulletin will be reviewed regularly and be updated as scientific and medical literature becomes available. For more information on how Medical Policy Bulletins are developed, go to the About This Site section of this Medical Policy Web site.

### Policy

Coverage is subject to the terms, conditions, and limitations of the member's contract.

#### MEDICALLY NECESSARY

NEWLY DIAGNOSED GLIOBLASTOMA WHEN USED IN ADJUVANT TREATMENT  
Alternating **electric** tumor treating **fields** (TTFields) are medically necessary and, therefore, covered for adult individuals (22 years of age or older) with newly diagnosed glioblastoma, when the individual meets all of the following criteria:

- Histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma)
- Tumor located in the supra-tentorial region of the brain
- Karnofsky Performance Score above 60
- Completed standard therapeutic options, such as maximum safe debulking surgery, concomitant temozolomide, or radiotherapy
- TTFields is prescribed with adjuvant temozolomide (maintenance)
- Willingness to use the TTFields device daily for at least 18 hours

RECURRENT GLIOBLASTOMA WHEN USED AS A MONOTHERAPY  
Alternating **electric** TTFields are medically necessary and, therefore, covered when used as a monotherapy for adult individuals (22 years of age or older) with recurrent glioblastoma, when the individual meets all of the following criteria:

- Histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma)
- Tumor located in the supra-tentorial region of the brain
- Karnofsky Performance Score above 60
- Completed standard therapeutic options, such as maximum safe debulking surgery or systemic chemotherapy or irradiation
- Willingness to use the TTFields device daily for at least 18 hours

#### NOT MEDICALLY NECESSARY



TTFields are considered not medically necessary and, therefore, not covered because the available published peer-reviewed literature does not support their use for the treatment of individuals with glioblastoma who have any of the following: an implanted pacemaker, programmable shunts, defibrillator, deep brain stimulator, other implanted devices in the brain, documented clinically significant arrhythmias, or evidence of increased intracranial pressure.

EXPERIMENTAL/INVESTIGATIONAL

All other uses of TTFields are considered experimental/investigational and, therefore, not covered because their safety and/or effectiveness cannot be established by review of the available published peer-reviewed literature.

REQUIRED DOCUMENTATION

The Company may conduct reviews and audits of services to our members regardless of the participation status of the provider. Medical record documentation must be maintained on file to reflect the medical necessity of the care and services provided. These medical records may include but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

PRESCRIPTION (ORDER) REQUIREMENTS

Before submitting a claim to the Company, the supplier must have on file a timely, appropriate, and complete order for each item billed that is signed and dated by the professional provider who is treating the member. Requesting a provider to sign a retrospective order at the time of an audit or after an audit for submission as an original order, reorder, or updated order will not satisfy the requirement to maintain a timely professional provider order on file.

PROOF OF DELIVERY

Medical record documentation must include a contemporaneously prepared delivery confirmation or member's receipt of supplies and equipment. The medical record documentation must include a copy of delivery confirmation if delivered by a commercial carrier and a signed copy of delivery confirmation by member/caregiver if delivered by the DME supplier/provider. All documentation is to be prepared contemporaneous with delivery and be available to the Company upon request.

CONSUMABLE SUPPLIES (WHEN APPLICABLE)

The durable medical equipment (DME) supplier must monitor the quantity of accessories and supplies an individual is actually using. Contacting the individual regarding replenishment of supplies should not be done earlier than approximately seven days prior to the delivery/shipping date. Dated documentation of this contact with the individual is required in the individual's medical record. Delivery of the supplies should not be done earlier than approximately five days before the individual would exhaust their on-hand supply.

If required documentation is not available on file to support a claim at the time of an audit or record request, the durable medical equipment (DME) supplier may be required to reimburse the Company for overpayments.

Guidelines

Tumor treating **fields** (TTFields) for the treatment of newly diagnosed and/or recurrent glioblastoma (GBM) utilizes a portable battery or power supply operated device which produces alternating **electrical fields** within the human body. TTFields are applied to individuals by **electrically** insulated surface transducer arrays. TTFields disrupt the rapid cell division exhibited by cancer cells.

TTFields are intended to harness **electric fields** to arrest the proliferation of tumor cells and to destroy them. The TTFields technology takes advantage of the special characteristics and geometrical shape of dividing cells, which make them susceptible to inhibiting cellular division during mitosis. The **fields** are said to alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used in the treatment of GMB has been specified to 200kHz.

KARNOFSKY PERFORMANCE STATUS (KPS)

A scale measuring the ability of individuals to perform ordinary tasks. KPS scores range from 0 to 100; a higher score means a person is better able to carry out daily activities.

KPS	Definition
100	Normal; no complaint; no evidence of disease
90	Able to carry on normal activity; minor signs of symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity of do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network® (NCCN®), a not-for-profit alliance of 27 leading cancer centers devoted to patient care, research, and education, is dedicated to improving the quality, effectiveness, and efficiency of cancer care so that patients can live better lives. NCCN® promotes the importance of continuous quality improvement and recognizes the significance of creating clinical practice guidelines



appropriate for use by patients, clinicians, and other health care decision-makers. NCCN® provides a clinical practice guideline appropriate for use in the treatment of glioblastoma, both as a new diagnosis and in recurrent disease.

NCCN® provide clinical practice guidelines for central nervous system cancers on a variety of prognostic factors, such as: age, good performance status (KPS=60) , MGMT promotor status (methylated or unmethylated/indeterminate). When the medically necessary criteria listed in this medical policy are met, the NCCN® clinical practice guidelines endorse the use of TTFields, as follows:

**IN THE TREATMENT OF NEWLY DIAGNOSED GLIOBLASTOMA**

Maximum resection + carmustine (BCNU) wafer with adjuvant treatments inclusive of standard brain RT (recommended dose is 60 Gy in 2.0 Gy fractions or 59.4 Gy in 1.8 Gy fractions) + concurrent temozolomide and adjuvant temozomide + alternating **electric field therapy**.

**IN THE TREATMENT OF RECURRENT GLIOBLASTOMA**

Resection with or without carmustine (BCNU) wafer AND palliative/best supportive care if poor performance, or systemic chemotherapy, or consider reirradiation (category 2B) or alternating **electric field therapy** for glioblastoma (category 2B).

**REGULATORY STATUS**

On April 8, 2011, the FDA gave premarket approval for the NovoTTF-100A system (NovoCure Inc. Portsmouth, New Hampshire) for the treatment of adult patients (22 years of age or older) with histologically confirmed glioblastoma multiforme (GBM), following histologically or radiologically confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical **therapy** for GBM after surgical and radiation options have been exhausted.

On October 5, 2015, the FDA expanded approval for Optune™ (formerly NovoTTF-100A) system for the treatment of adult patients with newly diagnosed, supra-tentorial glioblastoma following maximal debulking surgery and completion of radiation **therapy** together with concomitant standard of care chemotherapy.

**BENEFIT APPLICATION**

Subject to the terms and conditions of the applicable benefit contract, TTFields are covered as durable medical equipment (DME) under the medical benefits of most of the Company's products when the medical necessity criteria listed in this medical policy are met.

**Description**

Glioblastoma multiforme (GBM) is the most prevalent and most fatal malignant brain tumor in adults, accounting for nearly 15% of all brain cancers. GBMs account for 46.6% of all malignant tumors with 12,150 new cases predicted annually. Malignant gliomas are histologically heterogeneous and invasive tumors that are derived from neuroglia, or glial cells, whose primary responsibility is to support the central nervous system's neuron cells. GBMs are classified by the World Health Organization (WHO) as astrocytoma. The WHO provides a grading scale based on the most malignant regions of the tumors. Tumor grades depend upon degree of nuclear atypia, mitotic activity, microvascular proliferation, and necrosis, with increased anaplasia, corresponding to higher tumor grades. The 2007 WHO classification of GBM is a grade IV, indicating the most severe cancer grade, exhibiting rapid tumor growth leading to exceedingly poor prognosis. Eighty percent of individuals diagnosed with GBM will progress to recurrent disease, even after the initial surgical options have been exhausted. Survival expectancy for individuals with newly diagnosed GBM averages between 14.6 to 16.7 months with one-year survival rates of 35%. Following a GBM recurrence, the one-year survival rate is only approximately 20%, and median survival ranges from three to nine months.

Although the prognosis is dismal, the treatment options remain limited. The standard first-line treatment for a GBM is maximum surgical resection of the tumor. The National Comprehensive Cancer Network (NCCN®) has developed clinical practice guidance for the treatment of GBM. At present, the recommended treatment for an individual who is newly diagnosed with a histologically confirmed GBM is: maximum resection surgery, followed by radiotherapy (fractionated focal irradiation in daily fractions of 2 Gray [Gy] given 5 days per week for 6 weeks, for a total of 60 Gy). Gray is a unit of measurement for ionized radiation defined by the absorption of one joule of radiation per one kilogram of matter. In addition to radiotherapy, individuals are treated with concomitant continuous daily temozolomide (75 mg per square meter of body-surface area per day, 7 days per week from the first to the last day of radiotherapy), then subsequent cycles (6) of adjuvant temozolomide (150 to 200 mg per square meter for 5 days during each 28-day cycle). For disease recurrence, standard care includes surgical resection in combination with Gliadel® Wafer, stereotactic radiosurgery, and re-operation for additional tumor resection. Irrespective of the varying treatment protocols between the newly diagnosed and recurrent populations, GBM reoccurrence is still 80% and two-year survival rates remain a mere 27% following initial diagnosis. Acknowledging these dismal treatment outcomes, research has been conducted on new therapeutic agents for the treatment of glioblastoma. Stupp et al developed a new technology called tumor treating **fields** (TTFields) initially utilized and studied to treat the population with recurrent GBM disease.

TTFields is a technology utilizing **electric** activity through **fields** and currents to influence the of polarity of molecules, ions, and the cell membranes found in biological organisms to exert an effect on cellular process and impact cell division. By exposing cancer cells to alternating **electric fields** of low intensity and intermediate frequency, cellular polarity and ionic energy could be manipulated. This mechanism of action purported by TTFields (alternating **electric fields**) could selectively arrest cellular division (cytokinesis) in cancer cells by impairing normal mitosis and cytokinesis. TTFields are shown to have no effect on non-dividing cells, but to induce apoptosis in dividing cells. The **electric** ?elds interfere with cell division by causing misalignment of highly polarized subunits (microtubule monomers) in the mitotic spindle during the metaphase to anaphase transition and by dielectrophoretic movement of intracellular macromolecules and organelles during telophase. During cytokinesis, TTFields generate non-uniform intracellular **fields**, pulling organelles towards the neck that separates the newly forming daughter cells. In addition, TTFields interfere with the formation of the mitotic spindle by exerting forces on the charged tubulin subunits. Both processes lead to cell apoptosis and tumor growth inhibition. TTFields exert maximal effects when aligned to a cell's mitotic axis. As a cell's mitotic axis can occur randomly in any direction, additive cytotoxic effects are also observed when TTFields are applied in multiple sequential directions.

Individuals who utilize this technology for the treatment of GBM would need to place four transducer arrays onto their shaved scalp and connected to a portable, battery or power supply operated device (Optune, formerly the NovoTTF-100A system), which is preset to generate 200 kHz **electric fields** within the brain in two sequentially, perpendicular directions. The intensity of the **field** is also preset by the manufacturer at >0.7 V/cm. Treatment is intended to be continuous and take place in the home setting to allow the participants to maintain daily activities. Transducer arrays are supplied sterile, and prior to placement of the arrays, the scalp must be shaved carefully to limit the adverse effects (i.e., skin irritation, skin wounding). Although uninterrupted treatment is recommended, individuals can take treatment breaks of up to an hour, twice per day, for personal needs (i.e., shower).



The electrodes themselves are made from high dielectric constant insulated ceramic discs soldered to a flexible circuit board. The flexible printed circuit incorporates the components required for delivering the current for each ceramic plate and for measuring the temperature. At the set parameters, the electrodes are not reported to cause significant heating due to dielectric losses of the insulation or induced **fields** in the target tissue.

The Optune system contains a separate software component for the use of clinical treatment planning. The NovoTAL™ system is a workstation based software tool that uses MRI head morphology, tumor size and location measurements, and tissue dielectric properties to optimize the TTFields' distribution and intensity within the tumor by determining the specific region of the brain to treat with the placement of paired arrays. The planning software is intended for use by physicians certified to prescribe electronic TTFields used for the treatment of GBM.

PEER REVIEWED LITERATURE

Kirson et al (2004) evaluated 11 types of cancerous cell lines in more than 500 in vitro culture dishes. The researchers calculated growth rates of the cells and measured cell proliferation. In all cell lines reviewed, each culture dish was exposed to TTFields for a period of 24-hour intervals at 100 kHz (at an intensity of 1.0–1.4 V/cm), which resulted in significant inhibition of cell proliferation. To test the relationship between TTFields' intensity and inhibition of cell proliferation, Kirson et al exposed mouse melanoma and rat glioma cell lines to TTFields of different intensities between 1 and 2.5 V/cm. Furthermore, authors reported that the inhibitory effect of TTFields on cell proliferation increased as intensity increased until complete proliferation arrest was achieved at intensities of 1.4 and 2.25 V/cm in melanoma and glioma cells, respectively. The authors reported on the most relevant findings regarding the prolongation of mitosis, stating in treated cells, mitosis seemed to begin normally but was prolonged for variable periods of time before completing cleavage into two daughter cells. In the 500 cells evaluated, the authors reported TTFields had exemplary effect on the cellular process. In the cells treated with TTFields, mitosis was not complete within the standard 3 hours. TTFields treated cells displayed proliferation arrest, and mitosis lasted on average  $124 \pm 91$  min (mean Standard Deviation [SD], n= 53; 40–541 min), whereas in the controlled cells, the average mitosis duration was  $62 \pm 8$  min from cell rounding to cytokinesis with a mean SD of 12 and a range of 47-78 minutes. Their findings resulted in statistically significant prolongation of mitosis ( $P < 0.01$ , Mann-Whitney U test).

The authors reported in vivo studies with two animal tumor models. TTFields were generated between implanted (intradermal) wholly insulated wires placed on both sides of the tumor. The researchers placed two sets of paired identical insulated wires on the back of a mouse. The comparative in the mouse study was that only one of the pairs were connected to device, thus only exposing the area under the connected pair to TTFields treatment.

The researchers demonstrated that 100 KHz to 1 MHz alternating direction **fields** have significant specific effects on dividing cells. They reported that the areas treated with **electric field** of alternating direction provided evidence that all charges and polar molecules are subjected to forces of alternating direction so that ionic flows and dipole rotation oscillate. The basis of these effects during cytokinesis was shown to be that the unidirectional forces induced by disrupting mitotic spindle formation could result in physical disruption of the cell membrane and ultimately to apoptosis. During mitosis, exposure of cells to those **fields** results in one-fourth being destroyed as the formation of the cleavage furrow approached complete cell separation and violent membrane protrusions and cells exhibit disruption of microtubule spindle elements. Additionally, the authors reported that the direction of the placed **electrical** current dictates the magnitude of cellular disruption. Kirson et al concluded that when TTFields are placed parallel to the plane division, cells exhibited more mitotic failure. Placement of the TTFields arrays is an important instruction when the technology is indicated in the treatment of cancers.

TUMOR TREATING **FIELDS** FOR THE TREATMENT OF RECURRENT, SUPRA-TENTORIAL GLIOBLASTOMA MULTIFORME

Kirson et al 2007 evaluated a single arm, pilot trial study on the safety and efficacy of TTFields treatment that was performed on 10 participants with recurrent GBM. Efficacy analysis was performed for recurrent GBM persons focusing on time to disease progression (TTP), progression-free survival at 6 months (PFS6), and overall survival (OS) as the primary outcomes for individuals treated with the NovoTTF-100A device. Based on such a small sample size no statistical hypothesis tests were measured. This study measured progression-free survival at 6 months (PFS6), producing a result of 50% (23–77%; 95% confidence interval). Ninety-five percent confidence intervals of survival proportions were calculated using Kaplan–Meier survival curves. The initial pilot study reported two of the ten participants surviving beyond the follow-up period, with the longest participant living for 124.0 weeks, differing from historical averages.

The authored indicated that the pilot study demonstrated TTP and OS values that were more than double the reported historical medians, and reported that TTFields treatment resulted in one complete response which was tumor free, confirmed by MRI ten months after stopping treatment, and one partial response which was still responding seven months after stopping treatment. Both were still progression free two years from treatment initiation. In addition, one participant had minimal response, and four had stable disease for over 4 months before progressing, with the authors suggesting that the device could conceivably halt tumor growth.

The seminal trial, which led to the Food and Drug Administration (FDA) granting approval of TTFields, was a prospective randomized, phase III trial (EF-11) conducted by Stupp et al. (2012). The EF-11 trial assessed TTFields as a monotherapy, without chemotherapy, compared to physician's standard chemotherapy. 237 participants were randomly assigned in a 1:1 ratio to receive either TTFields, (n=120) or an active control entailing the best available chemotherapy prescribed at the local investigator's discretion (n= 117). Participants were all at least 24 years old, with an average age of 54, had Karnofsky performance scores of = 70 with limited other comorbidities. The study design reported that participants would receive baseline examinations and be tested monthly in laboratory. Magnetic resonance imagining (MRI) exams were repeated every second month, and quality of life questionnaires were completed every third month. The researchers allowed any number of prior treatments or recurrences of disease without limits. More than 85% of trial participants had failed two or more prior lines of chemotherapy (i.e., = second recurrence), and nearly 20% had failed (or had a recurrence) while being treated with bevacizumab prior to enrollment. Tumor response and progression were determined by a blinded central radiology review. This study was designed to demonstrate device superiority over the pharmaceutical control.

The trial's primary outcome was overall survival (OS). Secondary endpoints were: progression-free survival (PFS), the percentage of individuals alive and progression-free at 6 months (PFS6), 1-year survival rate, radiological response rate (RR), quality of life, and safety. OS and PFS were computed from randomization until event or censored at last follow-up utilizing Kaplan–Meier survival method, with 2-sided log rank statistics for comparison. The study had an 80 percent power at a significance level of 0.05 to detect a 60 percent increase in median OS (Hazard Ratio [HR] 0.63). All analyses were performed using the intent to treat population of all randomized participants, individuals lost to follow-up were censored at the time of last contact. Treatment compliance limitations were disproportionately observed in the study as only 78% (93/120) completed one full cycle of the TTFields. Nearly a quarter of all participants in the TTFields treatment arm were noncompliant and discontinued, or failed to begin treatment. 113 of 117 participants (97%) in the active control group started chemotherapy, and all but one person completed one full treatment course. The study presented with follow-up limitations. Twenty-one participants randomized to the control group failed to return to the treatment site, limiting information on disease progression and toxicity. Moreover, quality of life, a secondary



outcome of the study, was only available for assessment on 63 or 27% of trial participants.

Compliance was recorded for those individuals in the TTFields arm who began treatment (n=116) by device downloads. The downloads recorded the treatment duration that TTFields **therapy** was delivered to each participant. The observed median compliance rate was 86 percent (41–98%) during each treatment month, resulting into a mean duration use of 20.6 hours per day. The study acknowledged variance among the level of disease progression (i.e., first recurrence versus multiple) by the participants but failed to produce comparisons amongst the control groups. Missing these comparisons limits the study's ability to determine the overall effectiveness of the TTFields as a monotherapy. Participants received either single agent or a combination of chemotherapeutic regimens. The percentage breakdown for the chemotherapy agents prescribed were as follows: individuals received bevacizumab (31%), or irinotecan (31%), followed by nitrosoureas (25%), carboplatin (13%), temozolomide (11%) or various other agents (5%). However, the study reported that among individuals treated with the active chemotherapy control, survival was not significantly affected by the choice of chemotherapeutic agent ( $p = 0.66$ ).

The statistical analysis of the survival data was tested for proportional hazards and the assumption of proportionality met using the Cox proportional hazards regression model. The Cox model was performed in two steps; first, all protocol pre-specified baseline variables were tested directly for interactions with OS; then a reduced model was performed testing the effect of all variables with significant interaction ( $p < 0.05$ ) with OS together on the treatment effect of TTFields versus active chemotherapy. At a median follow-up of 39 months, 220 trial participants had succumbed to their disease (93%). The primary endpoint failed to demonstrate a significant increase in mean overall survival between the two treatments. Median survival failed to report statistical significance but was marginally higher in the TTFields group compared to active control chemotherapy (6.6 versus 6.0 months, respectively). One-year survival proportion was 20% in both groups and was unable to demonstrate superiority over common chemotherapy treatments. The 2- and 3-year survival rates were reported as 8% (95% CI, 4-13) and 4% (95% CI, 1-8) versus 5% (95% CI, 3-10) and 1% (95% CI, 0-3) for TTFields versus active control, respectively. The reported hazard ratio was 0.86 (95% CI, 0.66-1.12) in favor of TTFields ( $p = 0.27$ ), indicating that TTFields may be at least equivalent and trending toward an improvement as compared to active chemotherapy. The trial failed to report statistically significant device superiority. Participants were not restricted based on prior treatments or recurrences. Many of the participants presented with advanced disease at trial initiation. As many as 40% of participants were included after the third disease occurrence, possibly decreasing the potential benefit from treatment. Trial results showed TTFields as a monotherapy provided similar, not superior, efficacy as best physician's choice chemotherapy in individuals afflicted with recurrent GBM, albeit superior quality of life and less toxicity resulting from treatment with chemotherapy.

Secondary trial outcomes were presented without adjustment. Quality of life measures were assessed using the QLQ-C30 questionnaire with brain-specific module (BN-20), and the measurements were presented as the change from baseline to 3 months for each of the subscale domains and symptoms scale. The researchers reported that both cognitive and emotional functioning were higher in the TTFields group compared to the chemotherapy group, with no difference in global health. The researchers reported that more objective radiological responses (partial and complete responses) were seen in the TTFields group than in the active control chemotherapy group (14 versus 7, respectively). Progression-free survival (PFS) resulted marginally in favor of participants in the TTFields treatment group, with median PFS reported as 2.2 and 2.1 months for TTFields versus the active control group, respectively (HR 0.81, 95% CI 0.60 - 1.09; log rank  $p = 0.16$ ). Authors state progression-free survival at 6 month was 21.4 percent (95% CI 13.5 - 29.3) in the TTFields group and 15.1 percent (95% CI 7.8 - 22.3) in the active control group (chi squared  $p = 0.13$ ). The authors were unable to claim statistical significance for the trial outcomes.

This study was limited by the inability to be blinded, which could introduce bias and compromise the quality of life assessments. Participant knowledge of their active participation limits the pinnacle prognostic factor by creating bias. The disproportionate dropout rates are concerning. Many individuals stopped treatment prior to completing one month of treatment duration, and these individuals failed to be treated long enough to make substantial contributions to assist with determinations on device effectiveness. High rates of participant cross-over from chemotherapy into device treatment were observed in the study. Due to the nature of this disease and the dismal prognosis for individuals in this patient population, even marginal changes in overall survival and any increase in quality of life are clinically significant findings, as alternative to the current treatment modalities for individuals with recurrent GBM. Based on the slight improvement, trends observed in this trial suggest that treatment with TTFields may be considered an option.

Kanner et al performed a post hoc analysis to study the intent-to-treat (ITT) population in the TTFields treatment versus the best physician's choice chemotherapy. The authors report overall survival was significantly affected by duration that the TTFields device was worn. Not surprising, since this treatment is without a half-life and would require continuous application of the device to demonstrate a reduction in tumor growth. Stratifying population size to augment the desired results, the post hoc analysis measured outcomes within the population who fully completed at least one cycle (four weeks) of TTFields treatment. Based on those modifications, the researchers observed individuals who complied with treatment protocol of = 18 hours daily (n=92) had significantly longer overall survival medians, 7.7 versus 4.5 months than those who used treatment = 18 hours (n=28). Small sample sizes in the study diminish this power of the analysis, and the device may create adherence bias. However, a therapeutic response resulting in an observed mean overall survival increase of three months supports treatment effectiveness when compliance of the treatment protocol is adhered to.

A Patient Registry Dataset (PRiDe) followed 457 persons with recurrent GBM who received TTFields **therapy** was studied by Mrugala et al in a real-world, phase IV setting. Additional information on the safety and effectiveness of the **therapy** was assessed in the dataset. The primary outcome of the registry evaluated median overall survival, tolerability of the device, participant compliance and survival, and other prognostic factors. Mrugala reported overall survival (OS) and treatment using Kaplan-Meier methods and Cox proportional hazards model assessed participant characteristics and disease prognostic factors on survival. Evaluation was conducted with log-rank tests to compare OS and daily compliance, prior debulking surgery, Karnofsky Performance Score (KPS), number of recurrence, and prior bevacizumab use.

Overall survival between the PRiDe participants and those treated in the the seminal study with TTFields **therapy**, and physician's best chemotherapy, increased from 9.6 versus 6.6 versus 6.0 months, respectively. Overall survival rates at one- and two- years increased when compared to treatment arms (TTFields and chemotherapy) from the EF-11 study and PRiDe. As stated above, evidence supported daily compliance as a prognostic factor in TTFields **therapy**. Participants who achieved the recommended daily compliance of =18 hours a day had significantly longer ( $p=.0001$ ) overall survival --- 13.5 months versus 4.0 months when individuals reported less than =18 hours. Subgroup analysis of individuals treated at first recurrence (n=152) demonstrated the longest median overall survival, resulting in 20 months. The overall survival reported in the first recurrence population is similar to more recent studies on the newly diagnosed, suggesting that TTFields may be an option as an effective **therapy** in GBM recurrence, if treatment is initiated at earliest recurrence.

The registry failed to evaluate participant use of combination **therapy** with TTFields and prescription programs, such as chemotherapy and anti-vascular endothelial growth factor agents. Outside of a clinical trial, the lack of recording information on other medical management regimens for participants resulted in critically missed analyses in demonstrating the effectiveness of TTFields as a **therapy**, potentially misrepresenting the true effectiveness of the device in the largest studied population. The registry highlights compliance as a key finding, supporting the adaptation of TTFields; however, it failed to record compliance data for more than one-third of all device users. Device safety and tolerability was proven outside of observational settings. Consistent with other trials, the adverse event most commonly observed was



associated with device-related skin irritation.

The registry presented with limitations, including lack of quality of life measures, as these were excluded in the real world follow-up, an important prognostic factor in overall health outcome from the original trial. Heterogeneity limitations exist within the registry as 67% of the total population were male (n=309), possibly significant considering the need to shave a user's scalp for successful placement of the treatment arrays when utilizing this device.

**TUMOR TREATING FIELDS FOR THE TREATMENT OF NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME**

Stupp et al. 2015 conducted a multi-center, open-label, randomized phase III trial designed to evaluate the efficacy and safety of TTFields following chemoradiation with temozolomide (TMZ) for treatment of newly diagnosed glioblastoma. The trial enrolled 695 participants with histologically confirmed supra-tentorial glioblastoma, who were progression-free following debulking surgery or biopsy, and who have completed standard concomitant chemoradiotherapy with TMZ. These individuals were randomized (2:1) to receive combination **therapy** of TTFields plus temozolomide (TMZ) (n=466) or standard maintenance chemotherapy alone using TMZ (n=229). Randomization was stratified by participant characteristics: degree of resection, and O6-methylguanine-DNA methyltransferase (MGMT) methylation status. The primary outcome was progression-free survival (PFS) in the intent-to-treat (ITT) population and was assessed by independent reviewers (80% power; hazard ratio [HR], 0.78; allowing for 10% loss to follow-up; 2-sided a level of 0.05). This study investigated shifted overall survival to a secondary outcome but with equal power (HR, 0.76; 2-sided a = 0.05). To avoid an increase in the risk of a false positive result, overall survival was to only be tested statistically if the PFS was achieved.

In October, 2014, a safety monitoring committee reviewed the findings of an interim analysis reporting on the first 315 participants enrolled in the TTFields plus temozolomide (n=210) and temozolomide (n=105) treatment groups. Pre-specified endpoints were achieved in the intent-to-treat population. After a median follow-up of 38 months (18-60 months), the median PFS in the TTFields plus TMZ arm was 7.1 months from randomization (95% confidence interval [CI], 5.9 - 8.2 months) compared to 4.0 months (95 % CI, 3.3 - 5.2) in the control group ([HR] 0.62; 98.7% CI, 0.43 - 0.89; stratified log-rank, P= 0.001). Overall survival in the per-protocol analysis also showed significant improvement. The combination **therapy** group (n=196) resulted in median OS of 20.5 months (95% CI, 16.7 - 25.0 months) compared to 15.6 months (95% CI, 13.3 - 19.1 months) in the TMZ alone group (n=84) ([HR], 0.64; 99.4% CI, 0.42 - 0.98; P =0.004). Based on the results of the interim analysis, the trial was terminated, and participants in the control group were allowed to receive TTFields. The termination resulted in eleven individuals in the interim analysis and twenty-six participants overall to cross over and receive TTFields treatment. The study demonstrated the addition of TTFields to temozolomide treatment increased median progression-free survival in the ITT population by 3.1 months.

Per the study design, if tumor progression occurred, second-line chemotherapy was offered by local investigator's practice. Noteworthy, TTFields would continue in the treatment arm, until the second radiological confirmed progression, or clinical deterioration, for a maximum of 24 months. Brain imaging was routinely performed, initially at baseline with contrast-enhanced magnetic resonance imaging (MRI) at two weeks prior to treatment initiation, then in two-month intervals until second radiologically confirmed progression in all study participants. Two-thirds of the TTFields plus TMZ group (n=141) continued treatment with TTFields beyond first tumor progression. The trial design to stop at second tumor progression may have clinical importance when considering the progression of disease and the use of TTFields as a treatment option for individuals transitioning from a new diagnosis into recurrent GBM.

The authors reported median treatment duration of 5.8 months (1 - 58 months) with TTFields. Three-quarters (n=157) of enrollees receiving TTFields adhered to **therapy**. Protocol adherence was considered wearing the device = 18 hours per day on average during the first 3 treatment months. Further analyses in the ITT population showed the median overall survival was 19.6 months (95% CI, 16.6 - 24.4 months) in the TTFields plus temozolomide group compared to 16.6 months (95% CI, 13.6 - 19.2 months) in the temozolomide alone group ([HR],0.74 95% CI, 0.56 - 0.98; stratified log-rank P=0.03). The percentage of those affected by GBM alive at 2 years following enrollment was 43% in the TTFields plus temozolomide group and 29% in the TMZ alone group (P=0.006, a 14% increase of participants alive at two years in the treatment arm.

The original publication (interim analysis) of the EF-14 study was limited by the investigators stopping the trial earlier and allowing participant cross over. The interim analysis was completed after the initial 315 enrollees reached 18 month follow-up. The results in the initial per-protocol population only evaluated 196, 84 participants in the combination **therapy** (TTFields plus TMZ) or the TMZ alone arms, respectively. Additionally, as an open-label trial, no sham or placebo treatment was available for the control group. Investigators deemed the use of sham to be unethical, and impractical, and therefore the potential power of a placebo cannot be assessed. This may introduce adherence bias. The researchers acknowledge placebo bias would be unlikely to influence overall survival and progression-free survival. Following the original trial, which reported results that failed to provide evidence of statistically significant improvements in median overall survival, the primary study outcome shifted between the two seminal trials. In the original EF-11 trial, the primary endpoint was overall survival, and in this trial researchers adjusted the primary outcome to progression-free survival. The results of this study on newly diagnosed GBM, the addition of TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and improved overall survival.

Stupp et al 2017 reported on the final analysis inclusive of the entire trial population (n=695) from the open- label, randomized phase III trial designed to evaluate the effect of TTFields plus temozolomide (TMZ) versus maintenance TMZ alone on survival for individuals with glioblastoma. Stupp et al previously published the results from an interim analysis on the first 395 participants of the same study. The primary outcomes were consistent to the interim analysis.

The data set was locked on December 28, 2016, and the authors reported median treatment duration of 8.2 months (1 - 82 months) with TTFields. After a medium follow-up of 40 months (34 - 66 months), the median progression-free survival was 6.7 months (95% CI, 6.1 - 8.1 months) for individuals treated with combination **therapy** versus 4.0 months (95% CI, 3.8 - 4.4 months) for those treated with TMZ alone ([HR] 0.63, 95% CI, 0.52 - 0.76; P <0.001). The secondary outcome reported median overall survival duration of 20.9 months from randomization (95% CI, 19.3 - 22.7 months) in the TTFields plus TMZ group versus 16.0 months (95% CI, 14.0 - 18.4 months) for TMZ only ([HR],0.63; 95% CI, 0.53 - 0.76; P<0.001). Both were found to be statistically and clinically significant. Analyzing the percentage of living participants over selected time periods from randomization resulted in 46% alive at 2 years, 26% alive at 3 years, and 13% alive at 5 years in the combination **therapy** arm, compared to the TMZ only arm reporting 31% alive at 2 years (p <0.001); 16% at 3 years (P=0.009); and 5% at 5 years (P =0.004). Significant percentage increases across each selected time period favoring adjuvant TTField **therapy**.

The median time to randomization was equal among the treatment arms with 3.8 month (range 1.7 - 6.2) and 3.7 months (range, 1.4 - 6.3) in the combination **therapy**, and the TMZ alone treatment groups, respectively. Kaplan-Meier estimates for survival were accessed at 6 months for the rate of progression-free survival between the two treatment groups. The authors reported on progression-free survival at 6 months as 56% (95% CI, 51% - 61%) for the TTFields group and 37% (30% - 44%) with TMZ only (P < 0.001). Cox proportional hazards analyzed both overall survival and progression-free survival across factors: trial arms, age, sex, MGMT status, location, and county of residence. Results using Cox proportional hazards with 95% confidence intervals demonstrated several prognostic factors significantly improved OS; these



prognostic factors include: TTFields treatment group (HR, 0.63, 0.53 - 0.76, P<0.001), female sex (HR, 0.76, 0.63 - 0.92, P = .005), MGMT status (HR, 0.50, 0.41 - 0.62; P < 0.001), younger age (measured continuously, [HR], 0.978 per year, 0.969 - 0.985; P < 0.001), and higher KPS (as a categorical variable in 10 point increments P <0.001).

Interestingly, fifty-five percent of participants had a gross tumor resection (95% of tumor removed) and 13% had only a biopsy performed, results indicating the extent of excision was not statistically significant when investigating overall survival (P= 0.183). The addition of TTFields was not associated with an increase in systemic adverse events (AE) (48% versus 44%; P=0.58). Higher rates of AE found in the TTFields treated group were attributed to longer duration of TMZ treatment in the experimental group as a result of delayed disease progression. Investigators report inclusive criteria for TTFields treatment utilizing Karnofsky Performance Score (KPS). KPS is a scale measuring the ability of individuals to perform ordinary tasks. KPS scores range from 0 to 100; a higher score means a person is better able to carry out daily activities. The author reported time to sustain 10 point reduction in KPS significantly longer for the combination group versus the group treated with only TMZ (5.5 months; 95% CI, 5.0 - 6.3 months versus 3.9 months; 95% CI, 3.1 - 5.2 months, respectively; [HR], 0.80; 95% CI, 0.67 - 0.95; P =0.009).

Potentially important for future studies, a small majority of the experimental population (51%; n=237) continued TTFields treatment beyond first treatment progression. The investigators may want to evaluate, in the newly diagnosed population who elect to continue TTFields as a combination **therapy** beyond first progression, whether significant improvements are observed in progression-free survival and OS compared to the outcomes of the historical recurrent population. The recurrent population only has the option to utilize TTFields as a monotherapy. The largest study to date utilizing the TTFields technology presented with similar limitations as observed in the interim analysis (no sham, burden of use when utilizing the device). Another limitation in the final analysis was that quality of life data points were not recorded. Also, participant heterogeneity limitations exist since nearly 70% of the study participants were male and 89% were white.

The final analysis for the treatment of glioblastoma utilizing the TTFields technology demonstrated that the combination **therapy** of TTFields and temozolomide chemotherapy following standard concomitant TMZ and radiotherapy has shown to significantly improve progression-free survival and overall survival in the newly diagnosed population.

NovoCure Inc. of Portsmouth, New Hampshire (subsidiary of NovoCure Ltd., Haifa, Israel) was granted approval for the NovoTTF-100A system. The NovoTTF-100A Treatment Kit received US Food and Drug Administration (FDA) Premarket Approval on April 8, 2011 (P100034). The current supplement Optune™ System, which received FDA Premarket Approval on October 5, 2015 (P1000034/S013) was submitted to expand the indications for use: Optune™ System with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supra-tentorial glioblastoma following maximal debulking surgery and completion of radiation **therapy** together with concomitant standard of care chemotherapy.

In summary, TTFields has been demonstrated to be a safe and effective alternative treatment, and should be considered for individuals with either recurrent or newly diagnosed Glioblastoma. In 2015, The National Comprehensive Cancer Network® (NCCN®) clinical practice guidelines appropriateness in the treatment of central nervous system cancer for use of TTFields has shifted to consider category 3 in the recurrent population as a category 2B. A 2B category allows providers to consider the use of TTFields in treatment of recurrent disease. The NCCN® 2016 guidelines classifies alternating electronic **fields therapy** as a 2A grade for newly diagnosed glioblastoma individuals. NCCN® guidelines demonstrate TTFields used in concomitant treatment with adjuvant temozolomide following radiotherapy and concomitant temozolomide for the newly diagnosed. Indicating that use of TTFields could be used an initial treatment **therapy**, when prescribed with adjuvant temozolomide.

**TUMOR TREATING FIELDS IN OTHER INDICATIONS**

Researchers have initiated evaluations utilizing NovoCure's TTFields technology in the treatment of other solid tumor indications. The various populations actively being investigated include cancers such as: non-small cell lung (NSCLC), brain metastases (1-5; 1-10) from NSCLC, pancreatic, ovarian, mesothelioma, and high grade glioma and ependymoma in children. Each of these separate indications has been either recently completed or is actively being studied in phase II trials to determine safety and efficacy with this new modality. The trials range in size, n= 5 in the child study to 82 participants in the mesothelioma trial. Variance exists between the primary outcomes researched in each of the new indications. In the ovarian and pancreatic cancers, the primarily investigated outcome was device related adverse effects and feasibility based on compliance as a result of the individual's early discontinuation of treatment. The tumor location could be a factor in compliance. Toxicity was the principal measurement in the non-small cell lung cancer study, whereas overall survival was the primary outcome in the mesothelioma trial. All studies listed time to progression, or progression-free survival as a secondary endpoint.

Non-small cell lung cancer is currently under investigation, with participants actively enrolled into a prospective, randomized controlled phase III trial aimed to test the efficacy and safety of TTFields in combination with PD-1 inhibitors or docetaxel as a second-line treatment. The researchers will assess the overall survival of participants with the TTFields and docetaxel or PD-1 inhibitors versus docetaxel or PD-1 alone in a superiority study design. Interestingly, if the primary outcome fails, the researchers will evaluate overall survival of those treated with TTFields and docetaxel versus PD-1 inhibitors alone in a separate, more challenging non-inferiority study. This study has a completion date of December 2020.

Evaluation of a trial on the feasibility of Optune for children with recurrent or progressive supra-tentorial high-grade glioma and ependymoma cancers was initiated in early 2017. This trial aims to demonstrate use of the Optune device as a feasible treatment option in the pediatric population and report treatment-related toxicities assessed by Common Terminology Criteria for Adverse Events v4.0. A total of 25 children are expected to participate in this trial. This study was the first trial, inclusive of the pivotal trials, that utilizes the TTFields technology that was not funded or sponsored by the device manufacture, NovoCure, Ltd. The pediatric study is sponsored by Pediatric Brain Tumor Consortium, with support from the National Cancer Institute (NCI).

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-9, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)

N/A

Professional and outpatient claims with a date of service on or before September 30, 2015, must be billed using ICD-9 codes.  
Professional and outpatient claims with a date of service on or after October 1, 2015, must be billed using ICD-10 codes.

Facility/Institutional inpatient claims with a date of discharge on or before September 30, 2015, must be billed with ICD-9 codes.  
Facility/Institutional inpatient claims with a date of discharge on or after October 1, 2015, must be billed with ICD-10 codes.

ICD - 10 Procedure Code Number(s)

N/A

Professional and outpatient claims with a date of service on or before September 30, 2015, must be billed using ICD-9 codes.  
Professional and outpatient claims with a date of service on or after October 1, 2015, must be billed using ICD-10 codes.

Facility/Institutional inpatient claims with a date of discharge on or before September 30, 2015, must be billed with ICD-9 codes.  
Facility/Institutional inpatient claims with a date of discharge on or after October 1, 2015, must be billed with ICD-10 codes.

ICD -10 Diagnosis Code Number(s)

- C71.0 Malignant neoplasm of cerebrum, except lobes and ventricles
- C71.1 Malignant neoplasm of frontal lobe
- C71.2 Malignant neoplasm of temporal lobe
- C71.3 Malignant neoplasm of parietal lobe
- C71.4 Malignant neoplasm of occipital lobe
- C71.5 Malignant neoplasm of cerebral ventricle
- C71.8 Malignant neoplasm of overlapping sites of brain

HCPCS Level II Code Number(s)

- A4555 Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
- E0766 Electrical stimulation device used for cancer treatment, includes all accessories, any type

Revenue Code Number(s)

N/A

Policy History

07.03.26:

03/23/2018	This new policy has been issued to communicate the Company's coverage position.
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Version Effective Date: 03/23/2018  
Version Issued Date: 03/23/2018



Version Reissued Date: N/A



## Clinical UM Guideline

**Subject:** Electric Tumor Treatment Field (TTF)  
**Guideline #:** CG-DME-44  
**Status:** New

**Publish Date:** 06/28/2018  
**Last Review Date:** 05/03/2018

### Description

This document addresses electrical fields known as “tumor treatment fields (TTF)” that are created by low-intensity, intermediate frequency (100–200 kilohertz [kHz]) electric currents delivered to the malignant tumor site by insulated electrodes placed on the skin surface. TTF are felt to cause tumor cell death (apoptosis) by disrupting the assembly of microtubules during later stages of cell division.

### Clinical Indications

#### Medically Necessary:

The use of FDA approved devices to generate electric tumor treatment fields (TTF) to treat histologically-confirmed supratentorial glioblastoma (known also as glioblastoma multiforme [GBM] or World Health Organization [WHO] grade IV astrocytoma) is considered **medically necessary as adjunctive treatment** when **all** of the following criteria below are met:

- Initial treatment with debulking surgery or biopsy followed by chemoradiation with concomitant temozolomide and radiotherapy has been completed with no documented tumor progression\*; **and**
- TTF is used in combination with temozolomide; **and**
- TTF is initiated within 7 weeks from final dose of temozolomide and radiotherapy; **and**
- Individual has Karnofsky Performance Status score of 70 or higher **or** Eastern Cooperative Oncology Group (ECOG) performance status 0-1; **and**
- Individual or caregiver has been trained and is willing and able to apply and maintain the device at least 18 hours every day.

\*Progression is defined as tumor growth greater than 25% compared to smallest measured tumor area **or** the appearance of one or more new GBM lesions in the brain.

#### Not Medically Necessary:

The use of devices to generate electric tumor treatment fields (TTF) is considered **not medically necessary** when the criteria above are not met and for all other malignant tumors.

### Coding

*The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.*

#### CPT

77299 Unlisted procedure, therapeutic radiology clinical treatment planning [when specified as plan for using an electrical stimulation device for TTF]

#### HCPCS

A4555 Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only  
 E0766 Electrical stimulation device used for cancer treatment, includes all accessories, any type

#### ICD-10 Diagnosis

C71.0-C71.9 Malignant neoplasm of brain  
 Z85.841 Personal history of malignant neoplasm of brain

### Discussion/General Information

According to the NCI (2018), glioblastoma (WHO grade IV astrocytoma) is also known as GBM. The peak incidence for GBM occurs between the ages of 45 and 70 years. Glioblastoma is highly invasive and is the most frequently occurring brain tumor accounting for approximately 12% to 15% of all brain tumors and 50% to 60% of all astrocytic tumors. Giant cell glioblastoma and gliosarcoma are two histologic variants of glioblastoma multiforme. According to the NCCN (2018) GBM is the “deadliest brain tumor with only a third of patients surviving for one year and less than 5% living beyond 5 years.”

The Optune (formerly NovoTTF-100A System) was approved by the FDA in April 2011, as a novel device to treat adults age 22 years or older with GBM that recurs or progresses after receiving chemotherapy and radiation therapy. TTF technology is also



being studied as a treatment for other solid tumors such as non-small cell lung cancer and melanoma. There are published data from TTF use to treat tumors in pre-clinical trials and from small case series. However, the published evidence does not support that long term safety and efficacy of TTF has been established when used as a treatment of tumors other than GBM. On October 5, 2015 the FDA granted approval for use of Optune in combination with temozolomide to treat adults age 22 years or older with newly diagnosed, supratentorial GBM after maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

The use of electric fields and the corresponding effects upon living tissue has been studied in the laboratory and clinical settings. At very low frequencies alternating electric fields (below 1 kHz) cause membrane depolarization which stimulates excitable tissue (Kirson 2004, 2007, 2009; Salzberg, 2008). Electric fields in the tens of kHz to megahertz (intermediate frequency) alternate too fast to stimulate tissue and results in minute heating. Kirson and colleagues (2004) demonstrated targeted inhibitory effects on dividing cells with the application of alternating electric fields of very low intensity (less than 2 V/centimeter [cm]) and intermediate frequency, called TTF. Utilizing time-lapse microphotography of mouse melanoma cell cultures, unique cellular processes as a result of TTF exposure were identified. Prolongation of mitosis in TTF-treated cells was statistically significant, and one-quarter of the treated cells were destroyed. Cellular destruction was observed only in mitotic cells, and cells at rest (quiescent) remained intact, both functionally and morphologically. Nuclear rotation was also observed in TTF-treated cell cultures. Microtubules, in the form of spatially organized mitotic spindles in dividing cells, have very large electric dipole moments that may be disoriented by TTF forces. In the control cell cultures, 95% of the mitotic spindles were intact and exhibited normal features in cells undergoing mitosis compared to 50% of abnormal cell activity in TTF-treated cultures. The use of TTF was then applied in vivo, to two animal tumor models (adenocarcinoma and malignant melanoma cells). TTF-treated tumors were significantly smaller compared to the control tumor size, and the surrounding normal tissue was spared from injury. The encouraging preclinical data led to studies of electric TTF treatment in humans based on the principle that TTF results in disruption of the cell membrane and programmed cell death of cancer cells.

### ***Glioblastoma Multiforme (GBM)***

The current standard of treatment for newly diagnosed GBM consists of tumor resection followed by daily low-dose temozolomide administered concurrently with external beam radiotherapy followed by adjuvant temozolomide with alternating electric field therapy (NCCN, 2018). Radiochemotherapy is followed by adjuvant temozolomide given for 6 to 12 months. The prognosis for individuals with GBM is poor, with a 1-year survival rate of less than 40%.

The U.S. Food and Drug Administration (FDA) approved the premarket approval application (PMA) for NovoTTF<sup>TM</sup>-100A System (NovoCure<sup>TM</sup> Ltd., Portsmouth, NH; Haifa, Israel) in 2011. The device is now marketed as Optune<sup>TM</sup> (NovoCure Ltd., Portsmouth, NH, Haifa, Israel). Optune is a portable, non-invasive device that is designed for the delivery of TTF to the head. The device is considered to be an alternative to standard medical therapy for GBM after surgical and radiation treatment options are exhausted. Initially, Optune (NovoTTF) was approved as a solitary treatment for adults (22 years of age or older) with histologically-confirmed, recurrent GBM in the supratentorial region of the brain after receiving chemotherapy. On October 5, 2015, the FDA approved the use of Optune in combination with temozolomide for the treatment of adults with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and radiation therapy.

Stupp and colleagues (2015) evaluated the safety and efficacy of TTF in individuals with newly diagnosed GBM following chemoradiation therapy. In a multi-center clinical trial, 695 individuals were randomized (2:1) to either TTF with temozolomide or temozolomide alone. The primary endpoint was identified as progression-free survival (PFS) in the intent-to-treat (ITT) population (significant threshold,  $p \leq 0.01$ ). An interim analysis was designed into the study to be conducted on the first 315 participants who had completed at least 18 months of follow-up. At interim analysis, the median PFS in the TTF plus temozolomide group was 7.1 months (95% confidence interval [CI], 5.9-8.2 months) compared to 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide group (Hazard Ratio [HR] 0.62; 98.7% CI, 0.43-0.89; stratified log-rank,  $p=0.001$ ). The secondary endpoint, the overall survival (OS) in the per-protocol population also showed significant improvement in the treatment group versus control. Median overall survival in the per-protocol population in the TTF plus temozolomide group versus the temozolomide alone group was 20.5 months (95% CI, 16.7-25.0 months) and 15.6 months (95% CI, 13.3-19.1 months) respectively (HR, 0.64; 99.4% CI, 0.42-0.98;  $p=0.004$ ). Based on the interim analysis results, the study was terminated and individuals in the control group were offered TTF in addition to temozolomide. A total of 11 individuals crossed over and began using TTF. With the exception of a higher incidence of localized skin reactions in the TTF plus temozolomide group, the incidence, distribution, and severity of adverse events were similar across both treatment groups. This trial does contain a few limitations. As enrollment was not initiated until following radiochemotherapy, this initial phase of treatment is subject to variability. Participants were excluded from participation for progression during early radiotherapy; therefore, those with a very poor prognosis were not included in the sample population. In addition, as TTF was continued beyond tumor progression, there was additional data on this group, increasing the potential for reporting bias. The final analysis of the data was consistent with the interim analysis results (Stupp, 2017).

Stupp and associates (2012) conducted a phase III, multinational, randomized controlled pivotal clinical trial upon which the initial PMA was based. Between September 2006 and May 2009, 28 clinical centers enrolled 237 adult participants with relapsed or progressive GBM despite conventional therapy (e.g., surgery and chemo-radiotherapy followed by chemotherapy). A total of 120 participants were randomized in a 1:1 ratio to receive monotherapy with NovoTTF treatment and 117 participants were randomized to the group treated with available best standard care (BSC) chemotherapies as practiced at each of the participating clinical centers. Chemotherapy agents considered as BSC during the trial included platinum-based chemotherapy (i.e., carboplatin); nitrosureas (BCNU); procarbazine; combination of procarbazine, lomustine and vincristine (PCV); temozolomide; and bevacizumab. A period of 28 days of treatment with NovoTTF was considered 1 full treatment course. Participants treated with NovoTTF were allowed to take breaks from treatment up to an hour, twice per day for personal needs such as showers. The primary endpoint of the study was OS. Secondary endpoints included PFS at 6 months (PFS<sub>6</sub>), time-to-progression (TTP), 1-year survival rate, quality of life (QOL), and radiological response. Participants were seen in clinic monthly, and magnetic resonance imaging (MRI) was performed after 2, 4, and 6 months from initiation of treatment and subsequent



MRIs were done according to local practice until disease progression. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with the participants' caregivers were used to assess participant mortality rates.

Of the 237 enrollees, 8 participants (4 in each group) did not receive the assigned therapy. A total of 97% (116) of 120 enrollees in the NovoTTF group started treatment and 93 participants (78%) completed 1 cycle (4 weeks) of therapy. Discontinuation of TTF occurred in 27 participants due to noncompliance or the inability to handle the device. For each TTF treatment month, the median compliance was 86% (range 41-98%), which equaled a mean use of 20.6 hours per day. In the BSC (active control) group, 113 (97%) of the 117 assigned participants received chemotherapy and all completed 1 full treatment course with the exception of 1 individual. In the BSC cohort, 21 participants did not return to the site and details on disease progression and toxicity were not available. Stupp and colleagues (2012) noted the median survival of 6.6 months in the TTF group was marginally higher than 6 months in the BSC group (HR 0.86, 95% CI, 0.66–1.12;  $p=0.27$ ). For both groups, 1-year survival was 20%. The survival rates for 2 and 3 years were 8% (95% CI: 4, 13) and 4% (95% CI: 1, 8) versus 5% (95% CI: 3, 10) and 1% (95% CI: 0, 3) for the TTF cohort compared to the BSC cohort, respectively. With a median follow-up of 39 months, 93% (220 participants) had died. Objective radiological responses (partial response [PR] and complete response [CR]) were noted in 14 participants in the TTF group and 7 in the BSC group, with a calculated response rate of 14.0% (95% CI, 7.9-22.4%) compared to 9.6% (95% CI, 3.9-18.8%), respectively. Sixteen percent of the TTF participants had grade 1 and 2 contact dermatitis on the scalp, which resolved with topical steroids. BSC participants experienced grade 2-4 events by organ system related to the pharmacologic activity of chemotherapy agents utilized. QOL data were available in 63 participants (27%). Based on the Quality of Life Questionnaire-Core 30 (QLQ C-30) and Brain Cancer Module (BN-20) questionnaires, 5 out of 6 general scales and 7 of 9 symptom scales including nausea, vomiting, diarrhea, constipation and pain, QOL was consistently higher in NovoTTF than in the control group. There were no meaningful differences observed between the domains of global health and social functioning. The BSC cohort had a larger decrease in the negative effects of seizures than the TTF cohort. The self-reporting of QOL indicators may be influenced by bias for the treatment group (FDA Label, 2011; Stupp, 2012). Although the NovoTTF-100A device has received FDA approval, the pivotal trial did not achieve the primary endpoint of the study, which was improved survival with NovoTTF treatment in comparison to chemotherapy.

In an industry-sponsored study, Kirson and colleagues (2007) reported results of TTF treatment on various tumor cell lines and animal tumor models and noted "Optimal frequencies differed between cancer cell types." Additionally, the effects of a total of 280 weeks of TTF treatment on 10 individuals with recurrent GBM were reported in the pilot study. TTF treatment resulted in a median TTP of 26.1 weeks (range, 3-124 weeks) and the PFS6 of 50% (23-77% CI). The median OS was 62.2 weeks (range, 20.3-124.0 weeks). One individual achieved a CR and is free from tumor 10 months after stopping treatment, and 1 participant achieved and continues to maintain a PR 7 months after stopping treatment. The authors concluded TTF treatment is encouraging when compared to historical average PFS6 of  $15.3 \pm 3.8\%$  and average historical TTP of  $9.5 \pm 1.6$  weeks and an average OS  $29.3 \pm 6$  weeks. Mild to moderate contact dermatitis was reported in 9 out of 10 participants.

Results from an industry-sponsored pilot study of TTF alone and TTF in combination with chemotherapy for individuals with diagnosed GBM were reported (Kirson, 2009b). In this single arm study, the first group included 10 individuals with recurrent GBM after failure of maintenance temozolomide, and 10 individuals with newly diagnosed GBM treated with TTF combined with temozolomide were in the second cohort. All 20 individuals were treated for an average of 1 year (range 2.5-24 months) continuously. The first group was compared to a matched group of 18 concurrent controls who received salvage chemotherapy for relapsed/recurrent GBM. The TTF-chemotherapy group was compared to a matched group of 32 concurrent controls who received temozolomide alone. In addition, OS for both cohorts was compared to matched historical control data. Data for the first group were reported by Kirson and colleagues in 2007. For the group of 10 individuals with newly diagnosed GBM, PFS was significantly different (HR 3.32; 95% CI, 1.9-5.9;  $p=0.0002$ ) between the TTF-chemotherapy group compared to the matched concurrent and historical controls. The difference in OS was also significant ( $p=0.0018$ ). The authors concluded TTF may also be an effective sensitizer when used concurrently with chemotherapeutic agents.

Vymazal and colleagues (2015) analyzed the response patterns in individuals who exhibited an objective response in two previous studies in order to evaluate the baseline characteristics of those individuals who responded and to evaluate the relationship between compliance with use and efficacy outcomes. The analysis was completed on one pilot study ( $n=10$ ) and a phase III trial ( $n=237$ ) in which TTF was compared to standard chemotherapy. Between both studies, TTF was administered as monotherapy in 130 individuals. Across both trials, there was a 15% response rate (16/110 with a 4% CR rate). There were no significant differences in baseline characteristics between the responder and nonresponder groups. In those in which a response was noted, there was frequently a delayed response; the tumor would initially continue to grow before responding to treatment. Analysis supported that an increase in compliance was associated with better treatment response and longer OS. The extent of treatment response in those who exhibited a response was dependent on compliance ( $p<0.001$ ).

Treatment recommendations for brain tumors published by the National Comprehensive Cancer Network® (NCCN, 2018) and the National Cancer Institute (NCI, 2017) include surgical resection, radiation therapy and/or chemotherapy as treatment options. In 2014, the NCCN clinical practice guideline for CNS Tumors was updated and the consideration for alternating electric field therapy for individuals with recurrent, diffuse or multiple GBM was changed to a category 3 from the previous 2B level of evidence, denoting major disagreement on the appropriateness of the intervention. In May 2015, the NCCN clinical practice guideline was again revised to change the recommendation to consider alternating electric field therapy for glioblastoma from a category 3 back to a category 2B for recurrent disease. In 2018, NCCN added a category 1 recommendation for adjuvant alternating electric field therapy when used as an initial therapy along with temozolomide for individuals with anaplastic gliomas/glioblastoma with good performance status following standard radiotherapy and concurrent temozolomide. The NCI Adult Brain Tumors Treatment (PDQ®) (2018) does not include TTF treatment for recurrent GBM.

#### **Other Solid Tumors**

In addition to TTF treatment for brain tumors, this therapy has been studied in other types of malignancies, including breast cancer, non-small cell lung cancer (NSCLC) and pancreatic carcinoma. However, at this time, there are no studies which



support that the use of tumor treating fields for conditions other than GBM. The NCCN clinical practice guidelines do not include any recommendations regarding the use of electric TTF treatment for any condition other than GBM.

## Definitions

**Cytokinesis:** The cytoplasmic changes accompanying mitosis. The cleavage of the cytoplasm into daughter cells following nuclear division.

**Eastern Cooperative Oncology Group (ECOG) Performance Status:** A scale used to determine the individual's level of functioning. This scale may also be referred to as the WHO or Zubrod score which is based on the following scale:

- |   |   |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction  |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours                           |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours   |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair  |
| 5 | Dead  |

**Glioblastoma multiforme:** Stage IV glioblastoma, which includes WHO recognized variants, giant cell glioblastoma and gliosarcoma.

**Karnofsky Performance Status Score:** A 10 point scale used by healthcare providers to quickly evaluate how an individual is feeling on any given day.

- |     |   |
|-----|---|
| 100 | Able to work. Normal; No complaints; No evidence of disease.                        |
| 90  | Able to work. Able to carry on normal activity; Minor symptoms.                     |
| 80  | Able to work. Normal activity with effort; Some symptoms.                           |
| 70  | Independent; not able to work. Cares for self; Unable to carry on normal activity.  |
| 60  | Disabled; dependent. Requires occasional assistance; cares for most needs.          |
| 50  | Moderately disabled; dependent. Requires considerable assistance and frequent care. |
| 40  | Severely disabled; dependent. Requires special care and assistance.                 |
| 30  | Severely disabled. Hospitalized, death not imminent.                                |
| 20  | Very sick. Active supportive treatment needed.                                      |
| 10  | Moribund. Fatal processes are rapidly progressing                                   |

**Mitosis:** The process by which a single parent cell divides to make two new daughter cells. Each daughter cell receives a complete set of chromosomes from the parent cell, allowing the body to grow and replace cells.

**Progressive disease:** Disease that is growing, spreading or getting worse.

**Recurrent disease:** Disease that has recurred (come back), usually after a period of time during which the disease could not be detected. In the case of cancer, the disease may come back to the same place as the original (primary) tumor or to another place in the body: also called recurrence.

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#### Index

NovoTTF-100A System  
 NovoTTF-100L System  
 Optune  
 Tumor Treatment Field (TTF)

**The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.**

#### History

Status	Date	Action
New	05/03/2018	Medical Policy & Technology Assessment Committee (MPTAC) review.
New	05/02/2018	Hematology/Oncology Subcommittee review. Initial document development. Moved content of DME.00035 Electric Tumor Treatment Field (TTF) to new clinical utilization management guideline document with the same title.



## ***Tumor Treating Fields Therapy for Glioblastoma***

**Effective:** May 1, 2018

**Next Review:** February 201

**Last Review:** March 2018

### **IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

### **DESCRIPTION**

Glioblastoma multiforme is the most common and deadly form of malignant brain tumor in adults. It has a very poor prognosis and is associated with low quality of life during the course of treatment. Tumor treating fields therapy is a new, noninvasive technology that is intended to treat glioblastoma using electrical fields.

### **MEDICAL POLICY CRITERIA**

- I. Tumor treating fields (TTF) to treat primary supratentorial glioblastoma multiforme (GBM) may be considered **medically necessary** when all of the following are met:
  - A. Patient is 18 years of age or older; and
  - B. Documentation of histologically-confirmed primary supratentorial GBM; and
  - C. Following radiation and chemotherapy; and
  - D. Concurrent treatment with temozolomide (TMZ), unless TMZ has been ineffective, not tolerated, or is contraindicated.
- II. The use of mapping software to optimize TTF therapy may be considered **medically necessary** for GBM when patients meet criterion I. above.
- III. The use of TTF and/or TTF-associated mapping software is considered



**investigational** when the above criterion I. is not met.

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

## POLICY GUIDELINES

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Documentation of histologically-confirmed primary supratentorial glioblastoma multiforme (GBM)
- Radiation and chemotherapy history
- Documentation of Temozolomide (TMZ) maintenance treatment and response

## CROSS REFERENCES

None

## BACKGROUND

Glioblastoma multiforme (GBM) are the most common and deadly malignant brain tumor. Glioblastoma is the most common malignant primary brain tumor in adults, with a median age at diagnosis of 64 years.<sup>[1]</sup> GBMs are grade IV astrocytomas, the most deadly type of glial cell tumor, and are often resistant to standard chemotherapy. According to the National Comprehensive Cancer Network (NCCN), GBM is the "deadliest brain tumor with only a third of patients surviving for 1 year and less than 5% living beyond 5 years."<sup>[2]</sup>

The primary treatment for GBM is debulking surgery to remove as much of the tumor as possible. At that time, some patients may undergo implantation of the tumor cavity with a carmustine bis chloroethylnitrosourea (BCNU)-impregnated wafer.<sup>[2]</sup> Depending on the patient's physical condition, adjuvant radiation therapy, chemotherapy (typically temozolomide [TMZ]), or a combination of the two are sometimes given. After adjuvant therapy, some patients may undergo maintenance therapy with TMZ. In patients with disease that recurs after these initial therapies, additional debulking surgery may be used if recurrence is localized. Treatment options for recurrent disease include various forms of systemic medications such as bevacizumab, bevacizumab plus chemotherapy (e.g., irinotecan, BCNU/chloroethylnitrosourea (CCNU), TMZ), TMZ, nitrosourea, PCV (procarbazine, CCNU, and vincristine), cyclophosphamide, and platinum-based agents.<sup>[2]</sup> Response rates in recurrent disease are less than 10%, and progression-free survival rates at 6 months are less than 20%.<sup>[2,3]</sup>

## TUMOR TREATING FIELDS THERAPY

Tumor Treating fields (TTF) therapy is a new, noninvasive technology that is intended to treat GBM on an outpatient basis using electrical fields.<sup>[3-5]</sup> TTF therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis. TTF are proposed to inhibit rapidly dividing tumor cells by 2 mechanisms, arrest of cell proliferation and destruction of cells while undergoing division.<sup>[4,5]</sup>



The Optune™, formerly known as NovoTTF-100A™ System, (Novocure Inc.) has been approved by the U.S. Food and Drug Administration (FDA) to deliver TTF therapy. TTF therapy via the Optune™ is delivered by a battery-powered, portable device that generates the fields via disposable electrodes that are noninvasively attached to the patient's shaved scalp over the site of the tumor.<sup>[3,4]</sup> The device is used by the patient at home on a continuous basis (20-24 hours per day) for the duration of treatment, which can last for several months. Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living.<sup>[3,4]</sup>

## **NOVOTAL™ SYSTEM**

The NovoTAL™ (Transducer Array Layout) System (Novocure Inc.) is a proprietary software tool that produces a custom transducer array layout to optimize Optune therapy for each patient. The software accomplishes this by maximizing the intensity of Tumor Treating Fields (TTFields) based on MRI measurements of the head, tumor size and location(s) and optimizing TTFields distribution.

## **REGULATORY STATUS**

Optune™, (assigned the generic name of TTF) was approved by Food & Drug Administration (FDA) in April 2011 through the premarket approval (PMA) process.<sup>[6]</sup> FDA-approved indication for use are:

“Optune™ is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM).

Optune™ with temozolomide (TMZ), is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy. (FDA PMA approval granted in October 2015)

For the treatment of recurrent GBM, Optune™ is indicated following histologically- or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.”<sup>[7]</sup>

The NovoTAL™ System, was approved by the FDA in November 2013 through a PMA supplement for the Optune™ System. It is the software approved for use by physicians certified to prescribe the Optune™ System.

## **EVIDENCE SUMMARY**

### **PRIMARY GLIOBLASTOMA MULTIFORME**

In 2015, Stupp published interim results of a randomized controlled trial (RCT) regarding the safety and efficacy of TTF used in combination with temozolomide maintenance treatment after chemoradiation therapy for patients with GBM.<sup>[8]</sup> Patients were randomized in a 2:1 fashion to receive maintenance treatment with TTF and TMZ (n=466) or TMZ only (n=229). Study eligibility required patients to be 18 years or older, have a histologically confirmed supratentorial glioblastoma, be progression-free after having undergone maximal safe debulking surgery when feasible or biopsy, and have completed standard concomitant



chemoradiotherapy with TMZ. The median time from diagnosis to randomization was 3.8 months in both groups and patients were not blinded due to ethical concerns. TTF was delivered continuously (> 18 hours/day) via 4 transducers placed on the shaved scalp and TMZ (150-200 mg/m<sup>2</sup>/d) was given for 5 days of each 28-day cycle. Transducer array layouts were determined using the NvoTAL mapping software system for TTF fields to optimize field intensity within the treated tumor. A planned interim analysis was to be conducted on the first 315 patients at 18 months follow-up. The primary study endpoint was progression-free survival (PFS) in the intent-to-treat populations (with a significance threshold of .01) with overall survival (OS) in the per-protocol population (n = 280) as a powered secondary endpoint (significance threshold of .006). A total of 695 patients were enrolled across 83 centers; however the trial was terminated as it met its efficacy endpoints at interim analysis (median 38 months, 315 patients).

The interim analysis included the planned 315 subjects, with 210 in the TTF/TMZ group and 105 in the TMZ only group. The analysis was conducted at a median 38 months follow-up (range, 18-60 months). Prespecified per-protocol median PFS in the TTF/TMZ group was 7.1 months (95% CI, 5.9-8.2 months) compared to 4 months (95% CI, 3.3-5.2 months) in the TMZ only group (hazard ratio [HR], 0.62 [98.7% CI, 0.43-0.89]; P = .001). The median OS in the per-protocol population was statistically improved in the TTF/TMZ group (20.5 months; 95% CI, 16.7-25.0 months) compared to the TMZ only group (15.6 months; 95% CI, 13.3-19.1 months; HR, 0.64 [99.4% CI, 0.42-0.98]; P = .004). An additional analysis of the intention-to-treat population demonstrated and OS of 19.6 months (95% CI, 16.6-24.4 months) in the TTF/TMZ group compared to 16.6 months (95% CI, 13.6-19.2 months) in the TMZ only group (HR, 0.74 [95% CI, 0.56-0.98]; stratified log-rank p = .03). Forty-three percent of patients in the TTF/TMZ group were alive at 2-year follow-up, compared to 29% in the TMZ only group (p = .006).

These interim results demonstrate an approximate three-month improvement of PFS and five-month improvement of OS when TTF therapy is used concurrently with TMZ in patients with newly diagnosed GBM.

In 2017, Stupp published final results from this trial, including all 695 subjects.<sup>[9]</sup> From the time of randomization, median progression-free survival was 6.7 months in the TTF/TMZ group, and 4.0 months in the TMZ only group (HR, 0.63; 95% CI, 0.52-0.76; P < .001). Median overall survival was 20.9 months in the TTF/TMZ group as compared to 16.0 months in the TMZ only group (HR, 0.63; 95% CI, 0.53-0.76; P < .001). The application of TTF therapy in addition to TMZ treatment compared to TMZ treatment alone was not associated with an increase in adverse events (48% vs 44%, P = 0.58). Mild to moderate skin irritation was observed in 52% of patients who received TTF/TMZ treatment.

## **RECURRENT GLIOBLASTOMA MULTIFORME**

The literature on the efficacy of TTF therapy in patients with recurrent GBM consists of small, single-arm studies and two RCTs.

### **Randomized Controlled Trials**

The use of TTF and the corresponding effects on living tissue have been studied in clinical settings.<sup>[10-12]</sup> For example, in 2007, Kirson, reported the findings of a case study examining the effects of TTF therapy delivered by the NovoTTF-100A System in 10 patients with recurrent GBM.<sup>[10]</sup> Median time to progression (TTP) in these patients was 26.1 weeks and



median overall survival (OS) was 62.2 weeks. The authors noted that these TTP and OS values were more than double the reported medians of historical control patients. No device-related serious adverse events were seen after more than 70 months of cumulative treatment in all of the patients. The only device-related adverse event observed was a mild-to-moderate contact dermatitis beneath the field delivering electrodes. The primary limitation of this study was the use of historical controls, since the patients included may not be comparable on major clinical and prognostic features.<sup>[10]</sup>

These preliminary findings served as a basis for a 2012 prospective Phase III multinational RCT by Stupp, which was sponsored and funded by the manufacturer of the device (NovoCure). This study compared TTF therapy (delivered by the NovoTTF-100A System) to the best standard of care chemotherapy (active control).<sup>[3]</sup> Twenty-eight clinical centers (across 7 countries) enrolled 237 adult participants with relapsed or progressive GBM, despite conventional radiotherapy. Other prior treatments may have included surgery and/or chemotherapy. Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky performance status (KPS) of 80%. More than 80% of participants had failed 2 or more prior chemotherapy regimens ( $\geq$  second recurrence), and 20% had failed bevacizumab prior to study enrollment.<sup>[3]</sup>

Two hundred thirty-seven patients were randomized in a 1:1 ratio to receive TTF therapy only (n=120) or active control (n=117). The choice of chemotherapy regimens varied, reflecting local practice at each of the participating clinical centers.<sup>[3]</sup> Chemotherapy agents considered as active control during the trial included platinum-based chemotherapy (i.e., carboplatin); nitrosureas; procarbazine; combination of procarbazine, lomustine and vincristine (PCV); temozolomide; and bevacizumab. For patients assigned to the TTF group, uninterrupted treatment was recommended, although patients were allowed to take treatment breaks of up to 1 hour, twice per day, for personal needs (e.g., shower). In addition, patients assigned to the TTF group were allowed to take 2 to 3 days off treatment at the end of each of 4-week period (which is the minimal required treatment duration for TTF therapy to reverse tumor growth). A period of 28 days of treatment with TTF was considered 1 full treatment course.<sup>[3]</sup>

The primary study end point in this RCT was OS.<sup>[3]</sup> Secondary end points included progression-free survival (PFS) at 6 months, total time to progression (TTP), 1-year survival rate, quality of life (QOL), and radiological response. Participants were seen in clinic monthly, and magnetic resonance imaging (MRI) was performed after 2, 4, and 6 months from initiation of treatment, with subsequent MRIs done according to local practice until disease progression. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with the participants' caregivers were used to assess participant mortality rates.<sup>[3]</sup>

Ninety-seven percent (116) of 120 participants in the TTF group started treatment and 93 participants (78%) completed 1 cycle (4 weeks) of therapy. Discontinuation of TTF therapy occurred in 27 participants (22%) due to noncompliance or the inability to handle the device.<sup>[3]</sup> For each TTF treatment month, the median compliance was 86% (range, 41%-98%), which equaled a mean use of 20.6 hours per day. In the active control group, 113 (97%) of the 117 assigned participants received chemotherapy and all except 1 individual completed a full treatment course. Twenty-one participants (18%) in the active control group did not return to the treating site and details on disease progression and toxicity were not available.<sup>[3]</sup>

This RCT did not reach its primary end point of improved survival compared to active



chemotherapy.<sup>[3]</sup> With a median follow-up of 39 months, 220 participants (93%) had died. Median survival was 6.6 months in the TTF group compared to 6.0 months in the active control group (hazard ratio, 0.86; 95% confidence interval [CI], 0.66 to 1.12;  $p=0.27$ ). For both groups, 1-year survival was 20%. The survival rates for 2- and 3-year survival were 8% and 4%, respectively, for the TTF group versus 5% and 1%, respectively, for the active control group. PFS rate at 6 months was 21.4% in the TTF group, compared to 15.1% in the active control group ( $p=0.13$ ). Objective radiological responses (partial and complete response) were noted in 14 participants in the TTF group and 7 in the active control group, with a calculated response rate of 14.0% (95% CI, 7.9% to 22.4%) compared to 9.6% (95% CI, 3.9% to 18.8%), respectively. Sixteen percent of the TTF participants had grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids. Active control participants experienced grade 2-4 events by organ system related to the pharmacologic activity of chemotherapy agents utilized; severe (grades 3 and 4) toxicity was observed in 3% of participants.<sup>[3]</sup>

Longitudinal QOL data were available in 63 participants (27%).<sup>[3]</sup> There were no meaningful differences observed between the groups in the domains of global health and social functioning. However, cognitive, emotional, and role functioning favored TTF therapy, whereas physical functioning favored chemotherapy. Symptom scale analysis was in accordance to treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the TTF group.

In summary, this RCT failed to demonstrate the primary end point of improved survival with TTF therapy in comparison to chemotherapy.<sup>[3,13]</sup> Limitations of the trial included a somewhat heterogeneous patient population, with participants included after progression of 1 or several lines of chemotherapy, as well as the use of different chemotherapy regimens in the control group. Another limitation is the absence of a placebo/supportive care arm. In the setting of advanced disease, the supportive care arm would have been useful to gauge the safety and efficacy of treatment for both groups of patients. Treatments used in the active control arm (best standard of care chemotherapy) in the recurrent disease setting have previously demonstrated limited efficacy, thus limiting the ability to determine the true treatment effect of TTF. Data from a trial of TTF versus placebo, or of TTF plus standard chemotherapy versus standard chemotherapy alone would therefore provide a better assessment of treatment efficacy.

A further limitation was high dropout rates in both groups. For example, over 20% of participants in the active control group were lost at follow-up, and this may have underestimated the toxicity evaluation in this group. Similarly, over 20% of participants in the TTF arm discontinued treatment within a few days due to noncompliance or inability to handle the device. This implies that compliance might be an issue with TTF, as it requires the patient to continuously wear transducers on the shaved head. Finally, the number of patients who completed the QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators may have been subject to bias due to the lack of blinding.<sup>[3,6]</sup> Therefore, due to the numerous methodologic limitations, evidence from this trial is not sufficient to demonstrate that TTF therapy results in improved health outcomes for patients with recurrent GBM.

Post hoc subgroup analyses of these trial data have been published in abstract form comparing outcomes of patients between both groups who had failed bevacizumab prior to



study enrollment.<sup>[14,15]</sup> For example, Wong et al., published a subgroup analysis of the previously described RCT to determine characteristics of responders and nonresponders in the treatment and active control groups.<sup>[16]</sup> Tumor response was assessed by the Macdonald criteria. More patients in the TTF arm were considered responders (14/120 vs 7/117 in the chemotherapy arm.) Median response time was longer for those in the TTF arm than the chemotherapy arm (7.3 months vs 5.6 months,  $p < 0.001$ ), and there was a strong correlation (Pearson's  $r$ ) between response and OS in the TTF arm ( $p < 0.001$ ) but not in chemotherapy arm ( $p = 0.29$ ). Compared with the chemotherapy arm, a higher proportion of responders in the TTF arm had a prior low-grade histology (36% vs 0%). These differences in treatment responder groups suggest that TTF therapy may differentially benefit certain types of GBM; however, the small numbers of responders in both groups limits generalizations that can be drawn from this analysis.

## **Nonrandomized Studies**

A study published in late 2014 included OS data from 457 patients included in the Patient Registry Dataset (PRiDe), a postmarketing registry of all recurrent GBM patients who received NovoTTF therapy in a real-world, clinical practice setting in 91 centers.<sup>[17]</sup> The median OS rate in the PRiDe clinical practice dataset was reported as significantly superior to that attained in the TTF pivotal trial (9.6 months vs 6.6 months; HR=0.66, 95% CI, 0.05 to 0.86;  $p < 0.001$ ). One- and 2-year OS rates for TTF in PRiDe were significantly longer than those in the TTF group in the pivotal RCT (44% vs 20% at 1 year; 30% vs 9% at 2 years, respectively). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the pivotal RCT. These results, although promising, are limited by a lack of randomized comparison group with which to isolate the direct effect of TTF therapy upon symptom improvement and overall outcomes.

In addition, two very small case series have also been published of long-term survival (>6 years) with TTF therapy.<sup>[18,19]</sup> Since the approval of the NovoTTF device, additional case reports and very small case series ( $n=3-5$ ) have been reported.<sup>[20-22]</sup>

## **NOVOTAL™ SYSTEM**

### **Nonrandomized Studies**

In 2016, Connelly published a small feasibility study using the NovoTAL™ System with nonstandard non-contrast enhancement and advanced imaging.<sup>[23]</sup> All patients presented with gliomas (grades 2-4) and had previously received standard therapy prior to initiation of TTFields. A standard pre- and postcontrast MRI scan was acquired and used for TTFields treatment planning, in conjunction with other imaging modalities. Eight patients were reported on in this series: three underwent T2 imaging, one underwent FLAIR, one used diffusion weighted imaging, and one used MR-perfusion imaging. This case series demonstrates that treatment planning beyond the extent of contrast enhanced MRI is clinically feasible but it must be prospectively compared to standard treatment planning in a clinical trial setting, in order to determine the impact on patient outcomes.

In 2015, Chaudhry et al. evaluated physician performance in conducting transducer array layout mapping using the NovoTAL™ System compared with mapping performed by the Novocure in-house clinical team.<sup>[24]</sup> Fourteen physicians (seven neuro-oncologists, four medical oncologists, and three neurosurgeons) evaluated five blinded cases of recurrent glioblastoma. Concordance for each physician versus Novocure on 20 MRI measurements



was 0.96 (standard deviation, SD  $\pm$  0.03, range 0.90-1.00), indicating very high agreement between the two groups, indicating that physicians prescribing TTFields, when trained on the NovoTAL™ System, can independently perform transducer array layout mapping required for the initiation and maintenance of patients on TTFields therapy. This study did not address clinical utility.

## PRACTICE GUIDELINE SUMMARY

### NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on Central Nervous Systems Tumors (v.1.2017) recommend TTF therapy in conjunction with standard brain radiation therapy and current/adjuvant temozolomide for patients with supratentorial disease with good performance status. This is a category 3 recommendation. The panel conceded that data regarding TTF therapy is limited to evidence from the Stupp RCT which demonstrated similar survival in between groups. In addition, in the background section, the panel indicated that TTF therapy may be considered as a treatment option for recurrent GBM but not all panelists recommend treatment for these patients due to a lack of efficacy. The NCCN guideline does not address the use of TTF therapy recommendation section for patients with recurrent disease.<sup>[2]</sup>

## SUMMARY

The research on the safety and efficacy of tumor treating fields (TTF) therapy for patients with primary glioblastoma has some limitations. However, the small number of studies published do show that TTF therapy improves progression-free and overall survival in adult patients with primary glioblastoma multiforme (GBM) who are receiving concurrent temozolomide (TMZ) treatment. Therefore, TTF therapy may be considered medically necessary when criteria are met. TTF therapy in patients with recurrent glioblastoma multiforme (GBM) is limited to one randomized controlled trial which failed to demonstrate an improvement in overall survival or disease response. Due to insufficient research, the use of TTF therapy is considered investigational when criteria are not met, including but not limited to patients with recurrent glioblastoma.

There is limited research to show that the use of software to optimize tumor treating fields (TTF) therapy (e.g., the NovoTAL™ System) when used in conjunction with TTF therapy improves the outcomes of patients with glioblastoma compared to patients treated with TTF therapy alone. Despite these limitations, the use software to optimize TTF therapy in patients with glioblastoma may be medically necessary when criteria are met. Due to insufficient research, the use of TTF-associated mapping software is considered investigational when criteria are not met.

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## CODES

**NOTE:** There is no specific code for the NovoTAL System software program. While some may submit using CPT code 77261, the appropriate CPT code for this service is unlisted code 77299.

Codes	Number	Description
CPT	77261	Therapeutic radiology treatment planning; simple
	77299	Unlisted procedure, therapeutic radiology clinical treatment planning
HCPCS	A4555	Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only
	E0766	Electrical stimulation device, used for cancer treatment, includes all accessories, any type

**Date of Origin:** January 2014





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**Name of Policy:****Tumor-Treatment Fields Therapy for Glioblastoma**

Policy #: 536  
Category: DME

Latest Review Date: April 2018  
Policy Grade: C

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**Background/Definitions:**

*As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.*

*The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:*

- 1. The technology must have final approval from the appropriate government regulatory bodies;*
- 2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
- 3. The technology must improve the net health outcome;*
- 4. The technology must be as beneficial as any established alternatives;*
- 5. The improvement must be attainable outside the investigational setting.*

*Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:*

- 1. In accordance with generally accepted standards of medical practice; and*
- 2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
- 3. Not primarily for the convenience of the patient, physician or other health care provider; and*
- 4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*



## **Description of Procedure or Service:**

Glioblastoma multiforme is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during the course of treatment. Tumor-treating fields' (TTF) therapy is a new, noninvasive technology that is intended to treat glioblastoma using electrical fields.

## **Glioblastoma Multiforme**

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults, and they comprise approximately 15% of all brain and central nervous system tumors and more than 50% of all tumors that arise from glial cells. The peak incidence for GBM occurs between the ages of 45 and 70 years. GBMs are Grade IV astrocytomas, the most deadly type of glial cell tumor, and are often resistant to standard chemotherapy. According to the National Comprehensive Cancer Network, GBM is the "most lethal brain tumor with only a third of patients surviving for 1 year and less than 5% living beyond 5 years."

## **Treatment**

The primary treatment for patients newly diagnosed with GBM is to safely resect the tumor, and confirm a diagnosis; meanwhile, debulking the tumor to relieve symptoms of increased intracranial pressure or compression. At that time, some patients may undergo implantation with a carmustine (bischloroethylnitrosourea) (BCNU)-impregnated wafer. The cure rate with local treatment is very low; therefore, postsurgical treatment involves the use of adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of the 2 therapies. After adjuvant therapy, some patients may undergo maintenance therapy with temozolomide. Prognostic factors for success of therapy are age, histology, and performance status or physical condition of the patient.

No standard treatment exists for recurrent GBM. In patients with disease that recurs after these initial therapies, additional debulking surgery may be used if recurrence is localized. Treatment options for recurrent disease include various forms of systemic medications such as bevacizumab, bevacizumab plus chemotherapy (e.g., irinotecan, BCNU/chloroethylnitrosourea CCNU, temozolomide), temozolomide, nitrosourea, PCV (procarbazine, CCNU, and vincristine), cyclophosphamide, and platinum-based agents.

Fractionated external-beam radiotherapy after surgery is standard adjuvant therapy and also may be used to treat recurrent GBM. Response rates in recurrent disease are less than 10%, and progression-free survival rates at 6 months are less than 20%.

Testing for O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation has been proposed as a method to predict which patients with malignant gliomas may benefit from the use of alkylating agent chemotherapy, such as temozolomide. Data from randomized controlled trials have shown that MGMT promoter methylation is a predictor to responding to alkylating chemotherapeutic agents such as temozolomide. The response rate and overall survival with the use of temozolomide are higher in patients who have MGMT promoter methylation. *(See Medical Policy #582 on MGMT promotor methylation in malignant gliomas.)*



### *Tumor Treatment Fields*

Tumor-treating fields (TTF) therapy is a noninvasive technology that is intended to treat GBM on an outpatient basis using electrical fields. TTF therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis. Tumor-treating fields are proposed to inhibit rapidly dividing tumor cells by 2 mechanisms, arrest of cell proliferation and destruction of cells while undergoing division.

Optune®, formerly NovoTTF-100A System (Novocure, Haifa, Israel) is the only legally marketed TTF delivery system available in the United States. Optune is a portable battery or power supply operated device that produces alternating electrical fields within the human body. These fields are called tumor treatment fields and are applied to the patient's shaved head by means of electrically insulated surface transducer arrays, such that resistively coupled electric currents are not delivered to the patient. The device is used by the patient at home on a continuous basis (20-24 hours a day for the duration of treatment). Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living.

### *Karnofsky Performance Status (KPS)*

KPS is a standard way of measuring the ability of cancer patients to perform ordinary tasks. KPS scores range from 0 to 100; a higher score means a person is better able to carry out daily activities. For example, a KPS of 60 means a person requires occasional assistance, but is able to care for most of their personal needs. KPS may be used to determine a patient's prognosis, to measure changes in a patient's ability to function, or to decide if a patient could be included in a clinical trial.

### *Supratentorial*

Supratentorial refers to the upper portion of the brain comprised of the cerebrum and the diencephalon.

### *Temozolomide*

Temozolomide is an oral alkylating chemotherapy drug used in the treatment of some brain cancers. It is a first-line treatment for glioblastoma.

The FDA has not approved the use of electric TTF devices for indications other than GBM. Further studies are needed to determine the safety and long-term efficacy of electric TTF therapy for other types of cancer.



## **Policy:**

**Effective for dates of service on or after 04/26/2018:**

**Tumor-treating fields (TTF) therapy meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage to treat histologically-confirmed Supratentorial Glioblastoma (known also as glioblastoma multiforme [GBM], Grade IV) as adjunctive therapy when used according to FDA labeled indications, contraindications, warnings and precautions, and when ALL of the following criteria are met:**

- Initial treatment with debulking surgery or biopsy followed by chemoradiation with concomitant Temozolomide and radiotherapy have been completed; and
- TTF is used in combination with Temozolomide and
- Individual has Karnofsky Performance Status (KPS) score of  $\geq 60$  (requires occasional assistance, but is able to care for most of their personal needs); and
- Individual is age 22 or older and
- Individual or caregiver has been trained and is willing and able to apply the device daily; and
- Individual is willing to wear the device at least 18 hours daily.

**Tumor-treating fields (TTF) therapy meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage to treat recurrence of previously histologically confirmed Supratentorial Glioblastoma (known also as glioblastoma multiforme [GBM], Grade IV) when used according to FDA labeled indications, contraindications, warnings and precautions, and when ALL of the following criteria are met:**

- There is histologically or radiologically confirmed recurrence of supratentorial glioblastoma following treatment with surgery, chemotherapy, and/or radiation and
- TTF is used as monotherapy, and
- Individual has Karnofsky Performance Status (KPS) score of  $\geq 60$  (requires occasional assistance, but is able to care for most of their personal needs); and
- Individual is age 22 or older and
- Individual or caregiver has been trained and is willing and able to apply the device daily; and
- Individual is willing to wear the device at least 18 hours daily.

**Tumor Treatment Fields (TTF) therapy does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage when the criteria above are not met and for all other indications.**

**Computer software used for therapeutic radiology clinical treatment planning in conjunction with tumor treatment field (TTF) therapy does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered not medically necessary.**



**Effective for dates of service prior to 04/26/2018:**

**Tumor-treating fields (TTF) therapy for glioblastoma does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** for all indications, including but not limited to the following situations:

- As an alternative to standard chemotherapy for patients with advanced or recurrent glioblastoma multiforme;
- As an adjunct to standard maintenance therapy in patients with glioblastoma multiforme following initial treatment with surgery and/or radiotherapy.

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

**Key Points:**

The most recent literature review was through June 5, 2017. Following is a summary of the key literature.

Re-radiation options are limited for glioblastoma (GBM) patients who have received initial external-beam radiotherapy due to radiation tolerances. The tumors are locally invasive but do not metastasize, therefore, tumor treating fields (TTF) therapy as a locoregional intervention is proposed a treatment for GBM. Tumor treating fields (TTF) is proposed as a treatment for glioblastoma (GBM). For this review, 2 indications will be considered: (1) TTF as an alternative to chemotherapy in advanced or recurrent GBM and (2) TTF as an adjunct to maintenance treatment in patients following early treatment. Comparative trials are essential to determine efficacy in this area, and randomized controlled trials (RCTs) are needed to control for heterogeneity in the patient populations and other confounders of outcome. This review will include both RCTs and nonrandomized comparative trials.

**TTF as an Alternative to Chemotherapy for Progressive or Recurrent GBM**

**Randomized Controlled Trials**

The U.S. Food and Drug Administration (FDA) approval of the NovoTTF-100A system was based on a Phase III, multinational prospective RCT which was published in 2012 by Stupp et al. The Stupp et al study, which was sponsored and funded by the manufacturer of the device (NovoCure), compared TTF therapy (delivered by the NovoTTF-100A System) to the best standard of care chemotherapy (active control). Twenty-eight clinical centers (across 7 countries) enrolled 237 adult participants with relapsed or progressive GBM, despite conventional radiotherapy. Other prior treatments may have included surgery and/or chemotherapy. Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky performance status (KPS) of 80%. More than 80% of participants had failed 2 or more prior chemotherapy regimens ( $\geq$ second recurrence), and 20% had failed bevacizumab prior to study



enrollment. The performance of additional post recurrence debulking surgery was 28% in the TTF arm and 25% in the active treatment arm. Prior low-grade glioma progressing to glioblastoma was present in 8% of each trial arm at baseline.

Two hundred and thirty-seven patients were randomized in a 1:1 ratio to receive TTF therapy only (n=120) or active control (n=117). The choice of chemotherapy regimens varied, reflecting local practice at each of the participating clinical centers. Chemotherapy agents considered as active control during the trial included platinum-based chemotherapy (i.e., carboplatin); nitrosoureas; procarbazine; combination of procarbazine, lomustine and vincristine (PCV); temozolomide; and bevacizumab. For patients assigned to the TTF group, uninterrupted treatment was recommended, although patients were allowed to take treatment breaks of up to 1 hour, twice per day, for personal needs (e.g., shower). In addition, patients assigned to the TTF group were allowed to take 2 to 3 days off treatment at the end of each of 4- week period (which is the minimal required treatment duration for TTF therapy to reverse tumor growth). A period of 28 days of treatment with TTF was considered 1 full treatment course.

This study was designed as a superiority trial. The primary study endpoint in this RCT was overall survival (OS). Secondary endpoints included progression-free survival (PFS) at 6 months, time to progression (TTP), 1-year survival rate, quality of life (QOL), and radiological response. Participants were seen in clinic monthly, and magnetic resonance imaging (MRI) was performed after 2, 4 and 6 months from initiation of treatment, with subsequent MRIs done according to local practice until disease progression. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with the participants' caregivers were used to assess participant mortality rates.

One hundred sixteen (97%) of 120 participants in the TTF group started treatment and 93 participants (78%) completed 1 cycle (4 weeks) of therapy. Discontinuation of TTF therapy occurred in 27 participants (22%) due to noncompliance or the inability to handle the device. For each TTF treatment month, the median compliance was 86% (range 41-98%), which equaled a mean use of 20.6 hours per day. In the active control group, 113 (97%) of the 117 assigned participants received chemotherapy and all except 1 individual completed a full treatment course. Twenty-one participants (18%) in the active control group did not return to the treating site and details on disease progression and toxicity were not available.

Outcomes of this study are summarized in Table 1. The trial did not reach its primary endpoint of improved survival compared to active chemotherapy. With a median follow-up of 39 months, 220 participants (93%) had died. Median survival was 6.6 months in the TTF group compared to 6.0 months in the active control group (hazard ratio 0.86; 95% confidence interval [95% CI]: 0.66–1.12; p=0.27). For both groups, 1-year survival was 20%. The survival rates for 2- and 3-year survival were 8% and 4%, respectively, for the TTF group versus 5% and 1%, respectively, for the active control group. Progression-free survival rate at 6 months was 21.4% in the TTF group, compared to 15.1% in the active control group (p=0.13). Objective radiological responses (partial and complete response) were noted in 14 participants in the TTF group and 7 in the active control group, with a calculated response rate of 14.0% (95% CI: 7.9–22.4%) compared to 9.6% (95% CI: 3.9– 18.8%), respectively. Sixteen percent of the TTF participants had Grade 1 and 2 contact dermatitis on the scalp, which resolved with topical steroids. Active control



participants experienced Grade 2 to 4 events by organ system related to the pharmacologic activity of chemotherapy agents utilized; severe (Grades 3 and 4) toxicity was observed in 3% of participants.

Longitudinal QOL data were available in 63 participants (27%). There were no meaningful differences observed between the groups in the domains of global health and social functioning. Cognitive, emotional, and role functioning favored TTF therapy, whereas physical functioning favored chemotherapy. Symptom scale analysis was in accordance to treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea and vomiting were directly related to the chemotherapy administration.

Wong et al (2014) published a subgroup analysis of the previously described RCT to determine characteristics of responders and nonresponders in the treatment and active control groups. Tumor response was assessed by the Macdonald criteria. More patients in the TTF arm were considered responders (14/120 vs 7/117 in the chemotherapy arm.) Median response time was longer for those in the TTF arm than the chemotherapy arm (7.3 months vs 5.6 months,  $p < 0.001$ ), and there was a strong correlation (Pearson's  $r$ ) between response and OS in the TTF arm ( $p < 0.001$ ) but not in the chemotherapy arm ( $p = 0.29$ ). Compared with the chemotherapy arm, a higher proportion of responders in the TTF arm had a prior low-grade histology (36% vs 0%). Dexamethasone use among responders was also significantly lower than that in nonresponders in both NovoTTF-100A and BPC cohorts, responders had a lower daily dexamethasone usage than nonresponders. For the NovoTTF-100A cohort, the respective median and mean daily dexamethasone dose was 1.0 and 2.3 mg (95% CI, 0.8 to 3.8 mg) for responders and 5.2 and 6.8 mg (95% CI, 5.6 to 8.1 mg) for nonresponders ( $p = 0.002$ ). For the BPC chemotherapy cohort, the respective median and mean daily dexamethasone dose was 1.2 and 1.4 mg (95% CI, 0.3 to 2.4 mg) mg for responders and 6.0 and 7.2 mg (95% CI, 6.0 to 8.4 mg) mg for nonresponders ( $p = 0.004$ ). These differences in treatment responder groups suggest that TTF therapy may differentially benefit certain types of GBM; however, the small numbers of responders in both groups limits generalizations that can be drawn from this analysis.

**Table 1: Randomized Trial of TTF Versus Physicians' Choice Chemotherapy in Recurrent Glioblastoma: Principal Efficacy Results from Stupp et al**

Outcomes	TTF	Chemotherapy	Measure of Association, Significance
Median survival, mo	6.6	6.0	
Hazard ratio survival			0.86(95% CI, 0.66 to 1.12) favors TTF
Radiologic response(not all patients evaluated)	14%	9.6%	$p = 0.19$
Median PFS, mo	2.2	2.1	
Hazard ratio PFS			0.81(95%CI, 0.60 to 1.09) favors TTF

CI: confidence interval; PFS: progression-free survival; TTF: tumor treatment fields.

A second post hoc analysis of the TTF EF-11 pivotal trial data was performed to evaluate OS rates among patients who completed at least 1 complete course of TTF or chemotherapy. These investigators analyzed survival in what they referred to as a "modified ITT [intention-to-treat]" subgroup comprising 93 (78%) of 120 of the original TTF allocated group, versus 117 (100%) of

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117 of the original chemotherapy allocated group. This exercise revealed median OS of 7.7 months in the TTF modified ITT group compared with 5.9 months in the chemotherapy group (HR=0.69; 95% CI, 0.52 to 0.91; p=0.009). They also showed a trend relationship between proportion of patients with higher TTF compliance and median OS rates (p=0.039). The investigators suggest that TTF provides an OS benefit if used as intended in the FDA-approved label when compared with best chemotherapy. This post hoc analysis is limited as it was not prespecified in the study, includes only 78% of the original TTF allocated patients, and fails to control for noncompliance due to faster clinical deterioration of TTF recipients leading to treatment cessation.

#### Nonrandomized Comparative Studies

Two nonrandomized studies were identified that compared TTF treatment to standard care using historical controls. A study published in late 2014 included OS data from 457 patients included in the Patient Registry Dataset (PRiDe), a postmarketing registry of all recurrent GBM patients who received NovoTTF therapy in a real-world, clinical practice setting in 91 centers in the United States between October 2011 and November 2013. The median OS rate in the PRiDe clinical practice dataset was reported as significantly superior to that attained in the TTF EF-11 pivotal trial (9.6 months vs 6.6 months; HR=0.66, 95% CI, 0.05 to 0.86; p<0.001). One- and 2-year OS rates for TTF in PRiDe were significantly longer than those in the TTF group in the EF-11 trial (44% vs 20% at one year; 30% vs 9% at 2 years, respectively). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

Kirson et al (2007), for example, reported the findings of a case study examining the effects of TTF therapy delivered by the NovoTTF-100A System in 10 patients with recurrent glioblastoma multiforme (GBM). Median time to progression (TTP) in these patients was 26.1 weeks and median overall survival (OS) was 62.2 weeks. The authors noted that these TTP and OS values were more than double the reported medians of historical control patients. No device-related serious adverse events (AEs) were seen after more than 70 months of cumulative treatment in all of the patients. The only device-related AE observed was a mild-to-moderate contact dermatitis beneath the field delivering electrodes. The primary limitation of this study was the use of historical controls, since the patients included may not be comparable on major clinical and prognostic features.

#### Section Summary: Alternative to Chemotherapy in Advanced or Recurrent GBM

The single RCT for this indication reported that outcomes following TTF treatment are similar to outcomes following standard chemotherapy. Overall survival using TTF was noted at 6.6 months versus 6.0 months in the chemotherapy group. There was no placebo control group or supportive care treatment group, and the treatments used in the active control arm (best standard of care chemotherapy) have previously demonstrated limited efficacy. There are several methodologic limitations in the study. There was heterogeneity in the patient populations and heterogeneity in the chemotherapy regimens for the control group. Furthermore, there were more patients in the TTF group than in the control group who did not complete the treatment course, and patients in the TTF group received more courses of second line chemotherapy. People who used TTF in a clinical trial self-reported better quality of life with improved cognitive and emotional functioning compared to people who took chemotherapy. The other available published evidence is 2 nonrandomized comparative studies.



### TTF as an Adjunct to Standard Maintenance Care for GBM

In 2015, Stupp et al published a planned interim analysis of a multicenter, open-label RCT that evaluated maintenance therapy with TTF for GBM. This study enrolled patients with GBM who had completed standard treatment consisting of chemoradiotherapy, plus surgery if indicated. Patients were randomized in a 2:1 fashion to receive either TTF plus temozolomide (vs temozolomide alone). A Karnofsky Performance Score of 70% or higher was an additional inclusion criterion. At the time of the interim analysis, there were 210 patients randomized to TTF plus temozolomide and 105 patients randomized to temozolomide alone. The primary outcome was PFS analyzed by intention-to-treat; a secondary outcome was OS analyzed by per-protocol analysis.

Patients in the TTF group received continuous TTF delivered mainly in the home setting. Patients were trained on use of the device including changing the electrodes, and then treatment continued at home. Patients were encouraged to wear the device continuously, with the exception of short breaks to attend to personal needs. All patients were seen monthly for follow-up. MRI was performed every 2 months and QOL measures administered every 3 months. Tumor progression was adjudicated by a central review committee blinded to treatment group.

Planned interim analysis was performed at a median follow-up of 38 months (range, 18-60 months). Median PFS and median OS are summarized in Table 2.

**Table 2: TTF as an Adjunct to Standard Maintenance Care in GBM**

Group	N	Progression-Free Survival (95% CI)	Hazard Ratio (98.7 CI)	Overall Survival (95% CI)	Hazard Ratio (99.4%CI)
TTF + temozolomide	210(196 <sup>a</sup> )	7.1 mo (5.9 to 8.2 mo)	0.62 (0.43 to 0.89)	20.5 mo (16.7 to 25 mo)	0.64 (0.42 to 0.98)
Temozolomide alone	105(84 <sup>a</sup> )	4.0 mo (3.3 to 5.2 mo)		15.6 (13.3 to 19.1 mo)	

CI: confidence interval; TTF: tumor treatment fields

<sup>a</sup> Included in per-protocol analysis

There were a total of 35 (11%) dropouts during the study, 14 (6.7%) of 210 patients in the TTF group and 21 (20%) of 105 in the temozolomide alone group. Adherence to treatment was defined as wearing the device for at least 18 hours a day, and 157 (75%) of 210 patients met this criteria for adherence. The number of cycles of treatment with temozolomide differed between groups. The TTF group received a median of 6 cycles compared with a median of 4 cycles for the temozolomide alone group. The most common side effect of treatment was local skin irritation, which occurred in 43% of patients treated with TTF.

In October 2014, the trial independent data and safety monitoring committee reviewed the interim analysis, concluding that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended trial termination. The FDA-approved study termination and the trial was closed to recruitment in November 2014 after 695 of the planned 700 participants had been randomized. All patients in the control maintenance therapy arm were



could crossover to receive TTFs. At the time of the Stupp interim analysis, 35 control arm participants had crossed over.

The FDA considered the results of this analysis for the 2015 expanded approval of Optune®.

#### Section Summary: TTF as an Adjunct to Standard Maintenance Care for GBM

The single RCT for this indication reports that PFS is improved by 3.1 months and OS is improved by 4.9 months after the addition of TTF to standard maintenance therapy. Therefore, there may be a survival benefit associated with TTF for this indication. The single RCT has some methodologic limitations and the current publication is a planned interim analysis. The lack of a placebo group and the lack of blinding create the possibility of a placebo effect, even with the survival outcomes. There was a moderately high rate of dropouts overall (11%) and differential dropout between groups (6.7% in the TTF group vs 20% in standard maintenance group). Also, for the outcomes that were evaluated on a per-protocol basis, such as overall survival, there is the possibility of an adherence bias, in that patients who complete the treatment protocol may have better outcomes than patients who do not complete the protocol.

#### **Summary of Evidence**

For individuals who have advanced or recurrent GBM who receive TTF as an alternative to standard chemotherapy, the evidence consists of one RCT and non-randomized comparative studies. Relevant outcomes include overall survival, progression-free survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The single published RCT reported overall survival using TTF at 6.6 months versus 6.0 months in the chemotherapy group. This trial has several methodologic limitations, including the comparisons made include only an active control. There was high dropout, with >20% of patients in each group lost to follow-up, and for the quality of life outcomes only approximately 25% of enrolled patients had complete data. The 2 non-randomized studies were small and have limited validity due to differences in the patient populations treated with TTF and standard care. The evidence is sufficient to determine the effects of the technology on health outcomes.

For individuals who have GBM and who receive TTF as an adjunct to maintenance treatment following initial treatment with surgery and/or radiation, the evidence consists of one RCT. Relevant outcomes include overall survival, progression-free survival, quality of life, and treatment-related morbidity. The single RCT on this question reports that patients who receive TTF treatment plus temozolomide have longer progression-free survival (3.1 months) and overall survival (4.9 months) compared to patients receiving temozolomide alone. The trial has methodologic limitations including the lack of placebo control, differential dropout between groups, and the possibility of adherence bias for outcomes reported with per protocol analysis. The evidence is sufficient to determine the effects of the technology on health outcomes.

#### **Practice Guidelines and Position Statements**

The National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2018) include a recommendation for the treatment of glioblastoma. For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate MGMT promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric



currents therapy is a Category 1 recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a 2B recommendation...”

#### **U.S. Preventive Services Task Force Recommendations**

Not applicable.

#### **Key Words:**

NovoTTF-100A, NovoTTF, Novocure, TTF, Glioblastoma, GBM, Optune

#### **Approved by Governing Bodies:**

The NovoTTF-100A™ System (Novocure, Haifa, Israel; assigned the generic name of TTF) was approved by the FDA in April 2011 through the premarket approval process. The FDA-approved label reads as follows: “The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment, and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted.”

On September 28, 2014, FDA approved a request for Novocure to change its products name from NovoTTF-110A System to Optune™.

In October 5, 2015, FDA expanded the indication for Novocure’s use of Optune® in combination with temozolomide to include newly diagnosed GBM. The device was granted priority review status on May 8, 2015 because there was no legally marketed alternative device currently available for the treatment of newly diagnosed GBM that represents a life-threatening condition.

The FDA-approved label reads as follows: “This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.”

Based on the 2011 approval Optune® is also approved for the treatment of recurrent GBM in the supratentorial region of the brain after receiving chemotherapy. The device is intended for use as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

#### **Benefit Application:**

Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.



ITS: Home Policy provisions apply.

FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

### **Current Coding:**

#### **CPT:**

**77299** Unlisted procedure, therapeutic radiology clinical treatment planning

#### **HCPCS Codes:**

**A4555** Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only

**E0766** Electrical stimulation device used for cancer treatment, includes all accessories, any type

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### **Policy History:**

Medical Policy Panel, August 2013

Medical Policy Group, August 2013 (3): New policy; does not meet medical criteria for coverage and therefore considered investigational

Medical Policy Administration Committee, September 2013

Available for comment September 4 through October 19, 2013

Medical Policy Group, December 2013 (5): 2014 Coding Update- added new codes A4555 and E0766 to current coding effective 01/01/2014

Medical Policy Panel, August 2014

Medical Policy Group, August 2014 (5): Policy updated with literature review through June 26, 2014. Policy Description, Key Points, and References updated. Policy statement unchanged.

Medical Policy Panel, August 2015

Medical Policy Group, August 2015 (6): Updates to Description, Key Points, Approved by Governing Bodies and References; no change to policy statement

Medical Policy Group, May 2016 (6): Added Key Word "Optune"

Medical Policy Panel, August 2016

Medical Policy Group, August 2016 (6): Updates to Policy statement, Key Points, Practice Guidelines and Position Statements, Summary and References. No change in policy intent.

Medical Policy Group, September 2016 (6): Update to Practice Guidelines. No change to policy intent; remains investigational.

Medical Policy Panel, July 2017

Medical Policy Group, July 2017 (6): Updates to Description, Key Points, Practice Guidelines, Governing Bodies and References.

Medical Policy Group, April 2018 (6): Updates to Policy statement to allow coverage of TTF with criteria, Key Points, Practice Guidelines, Coding and References; full literature review to be completed with annual update.

Medical Policy Administration Committee May 2018

Available for comment May 4 through June 17, 2018

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*This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.*





MEDICAL COVERAGE GUIDELINES  
SECTION: Durable Medical Equipment (DME)

ORIGINAL EFFECTIVE DATE: 07/12/11  
LAST REVIEW DATE: 08/01/17  
LAST CRITERIA REVISION DATE: 09/27/16  
ARCHIVE DATE:

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## ELECTRIC TUMOR TREATMENT FIELDS

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Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Medical Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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**MEDICAL COVERAGE GUIDELINES**  
**SECTION: Durable Medical Equipment (DME)**

**ORIGINAL EFFECTIVE DATE: 07/12/11**  
**LAST REVIEW DATE: 08/01/17**  
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**ARCHIVE DATE:**

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## **ELECTRIC TUMOR TREATMENT FIELDS (cont.)**

### **Description:**

Electrical field therapy also referred to as Tumor Treatment Field (TTF) therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency using insulated electrodes placed on the skin surrounding the region of a malignant tumor to inhibit tumor growth and reduce tumor angiogenesis. TTF inhibit rapidly dividing tumor cells by arrest of cell proliferation and destruction of cells while undergoing division.

FDA-approved TTF devices, include, *but are not limited to*:

- NovoTTF™-100A System
- Optune®

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### **Criteria:**

- Electric tumor fields for the treatment of histologically-confirmed glioblastoma multiforme (GBM) is considered medically necessary as adjunctive treatment with documentation of **ANY** of the following:
  1. Newly diagnosed glioblastoma in combination with temozolomide following debulking surgery, completion of radiation therapy together with concomitant standard of care chemotherapy
  2. Confirmed recurrence of GBM
- Electric tumor treatment fields for the treatment of other malignant tumors or if criteria above not met is considered **experimental or investigational** based upon:
  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  4. Insufficient evidence to support improvement outside the investigational setting.



**MEDICAL COVERAGE GUIDELINES**  
**SECTION: Durable Medical Equipment (DME)**

**ORIGINAL EFFECTIVE DATE: 07/12/11**  
**LAST REVIEW DATE: 08/01/17**  
**LAST CRITERIA REVISION DATE: 09/27/16**  
**ARCHIVE DATE:**

## **ELECTRIC TUMOR TREATMENT FIELDS (cont.)**

### **Resources:**

**Literature reviewed 08/01/17. We do not include marketing materials, poster boards and non-published literature in our review.**

**The BCBS Association Medical Policy Reference Manual (MPRM) policy is included in our guideline review. References cited in the MPRM policy are not duplicated on this guideline.**

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10. Davies AM, Weinberg U, Palti Y. Tumor treating fields: a new frontier in cancer therapy. *Ann N Y Acad Sci*. May 9 2013.
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**MEDICAL COVERAGE GUIDELINES**  
**SECTION: Durable Medical Equipment (DME)**

**ORIGINAL EFFECTIVE DATE:** 07/12/11  
**LAST REVIEW DATE:** 08/01/17  
**LAST CRITERIA REVISION DATE:** 09/27/16  
**ARCHIVE DATE:**

## **ELECTRIC TUMOR TREATMENT FIELDS (cont.)**

### **Resources:** (cont.)

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MEDICAL COVERAGE GUIDELINES  
SECTION: Durable Medical Equipment (DME)

ORIGINAL EFFECTIVE DATE: 07/12/11  
LAST REVIEW DATE: 08/01/17  
LAST CRITERIA REVISION DATE: 09/27/16  
ARCHIVE DATE:

## ELECTRIC TUMOR TREATMENT FIELDS (cont.)

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### Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kwe'é atah nílínígíí Blue Cross Blue Shield of Arizona haada yit'éego bína'idíílkidgo éí doodago Háida bíjá anilyeedígíí t'áadoo le'é yína'idíílkidgo beehaz'áanii hółq díí t'áa hazaadk'ehjí háká a'doowołgo bee haz'ą doo baqah ilínígóó. Ata' halne'ígíí kojí' bich'í' hodíilnih 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thêm thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thông dịch viên, xin gọi 877-475-4799.

Arabic:

إن كان لديك أو لدى شخص تساعد أسئلة بخصوص Blue Cross Blue Shield of Arizona، فلديك الحق في الحصول على المساعدة والمعلومات الضرورية بلغتك من دون أية تكلفة. للتحدث مع مترجم اتصل بـ 877-475-4799.





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Case 1:20-cv-00194-WCG Filed 04/28/20 Page 298 of 1212 Document 11-2 1777





## Coverage Policy Manual

**Policy #:** 2013028  
**Category:** DME  
**Initiated:** August 2013  
**Last Review:** July 2018

### Tumor-Treating Fields Therapy

#### Description:

Glioblastoma multiforme is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during the course of treatment. Tumor-treating fields therapy is a new, noninvasive technology that is intended to treat glioblastoma using electrical fields.

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults, and they comprise approximately 15 percent of all brain and central nervous system tumors and over 50 percent of all tumors that arise from glial cells (NCI, 2013). The peak incidence for GBM occurs between the ages of 45 and 70 years. GBMs are grade IV astrocytomas, the most deadly type of glial cell tumor, and are often resistant to standard chemotherapy (NCI, 2013). According to the National Comprehensive Cancer Network (NCCN, 2013), GBM is the "deadliest brain tumor with only a third of patients surviving for one year and less than 5% living beyond 5 years" (NCCN, 2013).

The primary treatment for GBM is debulking surgery to remove as much of the tumor as possible. At that time, some patients may undergo implantation of the tumor cavity with a carmustine (bischloroethylnitrosourea [BCNU]) -impregnated wafer. Depending on the patient's physical condition, adjuvant radiation therapy, chemotherapy (typically temozolomide), or a combination of the two are sometimes given. After adjuvant therapy, some patients may undergo maintenance therapy with temozolomide. In patients with disease that recurs after these initial therapies, additional debulking surgery may be used if recurrence is localized. Treatment options for recurrent disease include various forms of systemic medications such as bevacizumab, bevacizumab plus chemotherapy (eg, irinotecan, BCNU/ chloroethylnitrosourea [CCNU], temozolomide), temozolomide, nitrosourea, PCV (procarbazine, CCNU, and vincristine), cyclophosphamide, and platinum-based agents. Response rates in recurrent disease are less than 10%, and progression-free survival rates at 6 months are less than 20%.

Tumor-treating fields (TTF) therapy is a new, noninvasive technology that is intended to treat GBM on an outpatient basis using electrical fields (Stupp, 2012; Davies, 2013; Pless, 2011). TTF therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis. Tumor-treating fields are proposed to inhibit rapidly dividing tumor cells by two mechanisms, arrest of cell proliferation and destruction of cells while undergoing division (Davies, 2013; Pless, 2011).

The NovoTTF-100A™ System (Novocure Ltd., Haifa, Israel) has been approved by the Food and Drug Administration (FDA) to deliver TTF therapy. TTF therapy via the NovoTTF-100A™ System is delivered by a battery-powered, portable device that generates the fields via disposable electrodes that are noninvasively attached to the patient's shaved scalp over the site of the tumor (Davies, 2013; Pless, 2011). The device is used by the patient at home on a continuous basis (20–24 hours per day) for the duration of treatment, which can last for several months. Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living (Davies, 2013; Pless, 2011).

#### Regulatory Status

The NovoTTF-100A™ System (assigned the generic name of TTF) was approved by FDA in April 2011 through the premarket approval process.<sup>6</sup> The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment, and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted" (US Food and Drug Administration, 2015).

On September 28, 2014, FDA approved a request for Novocure to change its products name from NovoTTF-110A System to Optune™ (Food and Drug Administration, 2014).



On May 11, 2015, FDA granted a priority review status for Novocure's premarket approval supplemental applications for the use of Optune in combination with temozolomide for newly diagnosed glioblastoma (Pharma, 2015).

**Coding**

There are no specific codes for this system or the initial application and instruction on use. The patient reapplies the transducer arrays at home after the initial instruction.

Effective in 2014, there are HCPCS codes for the system and the transducer arrays:

E0766: Electrical stimulation device, used for cancer treatment, includes all accessories, any type

A4555: Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only

**Policy/  
Coverage:**

**Meets Primary Coverage Criteria Or Is Covered For Contracts Without Primary Coverage Criteria**

Tumor treating fields therapy to treat glioblastoma multiforme meets member benefit certificate primary coverage criteria that there be scientific evidence of effectiveness as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

- Adult patients ≥18 years of age
- Karnofsky Performance Status score ≥70%
- Supratentorial tumor.

**Does Not Meet Primary Coverage Criteria Or Is Investigational For Contracts Without Primary Coverage Criteria**

Tumor treating fields therapy does not meet member benefit certificate primary coverage criteria that there be scientific evidence of effectiveness in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (eg, bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme.

For members with contracts without primary coverage criteria, tumor treating fields therapy, including but not limited to the following situations is considered investigational:

- As an adjunct to standard medical therapy (eg, bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme.

Investigational services are specific contract exclusions in most member benefit certificates of coverage.

**Rationale:**

This policy was created in August 2013 with a search of the MEDLINE database through June 3, 2013. The literature on the efficacy of TTF therapy consists of small, single arm studies and one RCT. Following is a summary of the key literature.

The use of TTF and the corresponding effects upon living tissue have been studied in clinical settings (Kirson, 2007; Kirson, 2009; Salzberg, 2008). Kirson and colleagues (2007), for example, reported the findings of a case study examining the effects of TTF therapy delivered by the NovoTTF-100A System in 10 patients with recurrent GBM (Kirson, 2007). Median time to progression (TTP) in these patients was 26.1 weeks and median overall survival (OS) was 62.2 weeks. The authors noted that these TTP and OS values were more than double the reported medians of historical control patients. No device-related serious adverse events (AEs) were seen after more than 70 months of cumulative treatment in all of the patients. The only device-related AE observed was a



mild-to-moderate contact dermatitis beneath the field delivering electrodes. The primary limitation of this study was the use of historical controls, since the patients included may not be comparable on major clinical and prognostic features (Kirson, 2007).

These preliminary findings served as a basis for a prospective phase III multinational randomized controlled trial (RCT) by Stupp and colleagues (2012), which was sponsored and funded by the manufacturer of the device (NovoCure). This study compared TTF therapy (delivered by the NovoTTF- 100A System) to the best standard of care chemotherapy (BSC, active control) (Stupp, 2012). The FDA approval of the NovoTTF-100A System was based on the results of this RCT. Twenty-eight clinical centers (across seven countries) enrolled 237 adult participants with relapsed or progressive GBM despite conventional radiotherapy. Other prior treatments may have included surgery and/or chemotherapy. Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky performance status (KPS) of 80%. More than 80% of participants had failed two or more prior chemotherapy regimens ( $\geq$  second recurrence) and 20% had failed bevacizumab prior to study enrollment (Stupp, 2012).

Two hundred and thirty-seven patients were randomized in a 1:1 ratio to receive TTF therapy only (n=120) or BSC (n=117). The choice of chemotherapy regimens varied, reflecting local practice at each of the participating clinical centers (Stupp, 2012). Chemotherapy agents considered as BSC during the trial included platinum-based chemotherapy (i.e., carboplatin); nitrosureas; procarbazine; combination of procarbazine, lomustine and vincristine (PCV); temozolomide; and bevacizumab. For patients assigned to the TTF group, uninterrupted treatment was recommended, although patients were allowed to take treatment breaks of up to an hour, twice per day, for personal needs (e.g., shower). In addition, patients assigned to the TTF group were allowed to take 2–3 days off treatment at the end of each of 4-week period (which is the minimal required treatment duration for TTF therapy to reverse tumor growth). A period of 28 days of treatment with TTF was considered one full treatment course (Stupp, 2012).

The primary study endpoint in this RCT was overall survival (OS) (Stupp, 2012). Secondary endpoints included progression free survival at six months, time to progression (TTP), one-year survival rate, quality of life (QOL), and radiological response. Participants were seen in clinic monthly, and magnetic resonance imaging (MRI) was performed after 2, 4 and 6 months from initiation of treatment, with subsequent MRIs done according to local practice until disease progression. Medical follow-up continued for two months after disease progression. Monthly telephone interviews with the participants' caregivers were used to assess participant mortality rates (Stupp, 2012).

Ninety-seven percent (116) of 120 participants in the TTF group started treatment and 93 participants (78%) completed one cycle (4 weeks) of therapy. Discontinuation of TTF therapy occurred in 27 participants (22%) due to noncompliance or the inability to handle the device (Stupp, 2012). For each TTF treatment month, the median compliance was 86% (range 41-98%), which equaled a mean use of 20.6 hours per day. In the BSC group, 113 (97%) of the 117 assigned participants received chemotherapy and all except one individual completed a full treatment course. 21 participants (18%) in the BSC group did not return to the treating site and details on disease progression and toxicity were not available (Stupp, 2012).

This RCT did not reach its primary end-point of improved survival compared to active chemotherapy (Stupp, 2012). With a median follow-up of 39 months, 220 participants (93%) had died. Median survival was 6.6 months in the TTF group compared to 6.0 months in the BSC group (hazard ratio 0.86; 95% confidence interval [95% CI], 0.66 – 1.12;  $p = 0.27$ ). For both groups, one-year survival was 20%. The survival rates for 2- and 3-years were 8% and 4% for the TTF group versus 5% and 1% for the BSC group. Progression-free survival rate at six months was 21.4% in the TTF group, compared to 15.1% in the BSC group ( $p = 0.13$ ). Objective radiological responses (partial and complete response) were noted in 14 participants in the TTF group and 7 in the BSC group, with a calculated response rate of 14.0% (95% CI, 7.9 - 22.4%) compared to 9.6% (95% CI 3.9 – 18.8%), respectively. Sixteen percent of the TTF participants had grade 1 and 2 contact dermatitis on the scalp, which resolved with topical steroids. BSC participants experienced grade 2-4 events by organ system related to the pharmacologic activity of chemotherapy agents utilized; severe (grades 3 and 4) toxicity was observed in 3% of participants (Stupp, 2012).

Longitudinal QOL data were available in 63 participants (27%) (Stupp, 2012). There were no meaningful differences observed between the groups in the domains of global health and social functioning. However, cognitive, emotional, and role functioning favored TTF therapy, whereas physical functioning favored chemotherapy. Symptom scale analysis was in accordance to treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the TTF group. Post-hoc



subgroup analyses of this trial data have been published in abstract form comparing outcomes of patients between both groups who had failed bevacizumab prior to study enrollment (Ram, 2010; Ram, 2011). Two very small case series have also been published of long-term survival (> six years) with TTF therapy (Rulseh, 2012; Vilano, 2013).

In summary, this RCT failed to demonstrate the primary endpoint of improved survival with TTF therapy in comparison to chemotherapy (Stupp, 2012; De Bonis, 2012). Limitations of the trial included a somewhat heterogeneous patient population, with participants included after progression of one or several lines of chemotherapy, as well as the use of different chemotherapy regimens in the control group. Another limitation is the absence of a placebo/supportive care arm. In the setting of advanced disease, the supportive care arm would have been useful to gauge the safety and efficacy of treatment for both groups of patients. Treatments used in the active control arm (best standard of care chemotherapy) in the recurrent disease setting have previously demonstrated limited efficacy, thus limiting the ability to determine the true treatment effect of TTF. Data from a trial of TTF versus placebo, or of TTF plus standard chemotherapy versus standard chemotherapy alone would therefore provide a better assessment of treatment efficacy. The latter study design is being used in an ongoing trial of TTF therapy in the treatment of newly diagnosed GBM patients.

A further limitation was high dropout rates in both groups. For example, over 20% of participants in the BSC group were lost at follow-up, and this degree of dropouts may have underestimated the toxicity evaluation in this group. Similarly, over 20% of participants in the TTF arm discontinued treatment within a few days due to noncompliance or inability to handle the device. This implies that compliance might be an issue with TTF as it requires the patient to continuously wear transducers on the shaved head and as a result. Finally, the number of patients who completed the QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators may have been subject to bias due to the lack of blinding (Stupp, 2012; FDA, 2011). Therefore, due to the numerous methodologic limitations, evidence from this trial is not sufficient to demonstrate that TTF therapy results in improved health outcomes for patients with recurrent GBM.

### **Ongoing Clinical Trials**

Two manufacturer-sponsored studies on NovoTTF-100A System for treatment of GBM currently are listed at online site ClinicalTrials.gov. Post-approval study of NovoTTF-100A in recurrent GBM patients (NCT01756729)

This study is a post-market non-randomized, concurrent control study, designed to confirm that the efficacy of the NovoTTF-100A System in patients with recurrent GBM treated in a real life settings following FDA approval is comparable to that of BSC chemotherapy patients. This trial has the estimated enrollment of 486 adult patients across two US sites. The primary outcome measure is OS at five years of follow-up. This study is currently recruiting participants with the estimated completion date of January 2018.

Effect of NovoTTF-100A together with temozolomide in newly diagnosed GBM (NCT00916409).

The study is a subsequent prospective multinational RCT designed to test the efficacy and safety of the NovoTTF-100A System, as an adjuvant to the best standard of care in the treatment of newly diagnosed GBM patients. This trial has the estimated enrollment of 700 adult patients across 79 sites. Trial participants randomized to the intervention arm will be treated continuously with the NovoTTF-100A device, in addition to temozolomide chemotherapy; patients in the control arm will be treated with temozolomide, as the best known standard of care for GBM patients. The primary outcome measure is progression free survival at five years; the secondary outcome measure is OS at five years. This study is currently recruiting participants with the estimated completion date of April 2015.

TTF therapy using the NovoTTF-100A System is also being studied as a treatment for other solid tumors including non-small cell lung cancer (NCT01755624).

### **Summary**

Tumor-treating fields (TTF) therapy is a new noninvasive technology using electrical fields for treating recurrent glioblastoma. The available evidence consists of small case series and one randomized controlled superiority trial based on the FDA-approved device. This trial had numerous methodologic limitations and failed to demonstrate an improvement in overall survival or disease response. There were some differences reported in quality-of-life, but this data was limited by a low response rate for QOL measures. In addition, the best standard chemotherapy protocols reported in the randomized controlled trial may not reflect current practice, given the increased use of bevacizumab and temozolomide for treatment of patients with recurrent glioblastoma. No data



were available to address a comparison to other third-line treatment modalities (i.e., radiation, surgery, combination therapy).

Further evidence from high-quality trials is needed to assess the long term safety and efficacy of TTF. There are currently ongoing clinical trials of the TTF therapy including an ongoing post-marketing non-inferiority study that will provide additional data on outcomes of interest.

**Practice Guidelines and Position Statements**

The National Comprehensive Cancer Network (NCCN) in their clinical practice guidelines on Central Nervous Systems Tumors (Version 2, 2013) has a Category 2B recommendation to consider the use of TTF therapy for persons with local, diffuse or multiple recurrences of GBM ("Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.") (NCCN, 2013). This recommendation was based on the RCT findings by Stupp and colleagues reported above.

**2014 Update**

A literature search conducted through July 2014 did not reveal any new information that would prompt a change in the coverage statement. The key identified literature is summarized below.

The FDA approval of the NovoTTF-100A system was based on a Phase III, multinational prospective RCT which was published in 2012 by Stupp et al. The Stupp et al study, which was sponsored and funded by the manufacturer of the device (NovoCure), compared TTF therapy (delivered by the NovoTTF-100A System) to the best standard of care chemotherapy (active control).<sup>3</sup> Twenty-eight clinical centers (across 7 countries) enrolled 237 adult participants with relapsed or progressive GBM, despite conventional radiotherapy. Other prior treatments may have included surgery and/or chemotherapy. Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky performance status (KPS) of 80%. More than 80% of participants had failed 2 or more prior chemotherapy regimens ( $\geq$  second recurrence), and 20% had failed bevacizumab prior to study enrollment.

Wong et al published a subgroup analysis of the previously-described RCT to determine characteristics of responders and nonresponders in the treatment and active control groups (Wong, 2014). Tumor response was assessed by the Macdonald criteria. More patients in the TTF arm were considered responders (14/120) compared to 7/117 in the chemotherapy arm.) Median response time was longer for those in the TTF arm than the chemotherapy arm (7.3 months vs 5.6 months,  $P=0.0009$ ), and there was a strong correlation (Pearson's  $r$ ) between response and OS in the TTF arm ( $P = 0.0002$ ) but not in chemotherapy arm ( $P=0.29$ ). Compared with the chemotherapy arm, a higher proportion of responders in the TTF arm had a prior low-grade histology (36% vs 0%). These differences in treatment responder groups suggests that TTF may differentially benefit certain types of GBM; however, the small numbers of responders in both groups limits generalizations that can be drawn from this analysis.

Rulseh et al reported long-term ( $>7$  year) survival in 4 out of 20 patients with GBM who were treated with TTF, while Villano et al describe one patient with recurrent GBM who was tumor-free more than 6 years after treatment with TTF (Rulseh, 2012).

Since the approval of the NovoTTF device, additional case reports and small case series have been reported. Elzinga and Wong reported a case of a patient who demonstrated improved tumor response to bevacizumab in a patient who also received TTF therapy (Elzinga, 2014). Another case series ( $n=3$ ) suggested that adjusting the size of the electrical fields may improve response in cases of local tumor progression (Turner, 2014).

The use of TTF therapy has been described in a number of case series. However, without evidence from additional high quality comparative studies, these studies provide limited additional evidence about whether TTF therapy improves outcomes when compared to currently-available therapy for GBM

**Ongoing Clinical Trials**

A search of the online database ClinicalTrials.gov in June 2014 identified the following ongoing studies to evaluate the use of tumor treating fields therapy, including one randomized controlled trial (RCT) and 3 nonrandomized studies:

A phase 3, open-label randomized trial **Effect of NovoTTF-100A Together With Temozolomide in Newly Diagnosed Glioblastoma Multiforme (GBM) (NCT00916409)** – to compare the NovoTTF-100A as an adjuvant to the best current standard of care to standard of care alone in patients with newly-diagnosed GBM. Trial



participants randomized to the intervention arm will be treated continuously with the NovoTTF-100A device, in addition to temozolomide chemotherapy; patients in the control arm will be treated with temozolomide, as the best known standard of care for GBM patients. The primary outcome measure is PFS at 5 years; the secondary outcome measure is overall survival at 5 years. Enrollment is planned for 700 patients; the planned study completion date is January 2015.

A postmarket nonrandomized, concurrent control study, **Post-approval Study of NovoTTF-100A in Recurrent GBM Patients (NCT01756729)** –designed to confirm that the efficacy of the NovoTTF-100A System in patients with recurrent GBM treated in a real-life settings following FDA-approval is comparable to that of control chemotherapy patients. The primary outcome measure is overall survival at 5 years of follow-up. Enrollment is planned for 486 patients; the planned study completion date is January 2018.

A phase 2, nonrandomized, safety/efficacy study, **NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma (NCT01894061)** –to evaluate the role of bevacizumab with the NovoTTF-100A in the treatment of glioblastoma. Enrollment is planned for 40 patients; the planned study completion date is December 2015.

A phase 2, nonrandomized, efficacy study, **NovoTTF Therapy in Treating Patients With Recurrent Glioblastoma Multiforme (NCT01954576)** – to evaluate NovoTTF in patients with recurrent or progressive tumor growth. Enrollment is planned for 30 subjects; the planned study completion date is May 2018.

### 2015 Update

A literature search was conducted using the MEDLINE database through July 2015. There was no new literature identified that would prompt a change in the coverage statement.

The following is a summary of the key identified literature.

A second post hoc analysis of the TTF EF-11 pivotal trial data was performed to evaluate OS rates among patients who completed at least 1 complete course of TTF or chemotherapy (Kanner, 2014). These investigators analyzed survival in what they referred to as a “modified ITT [intention to treat]” subgroup comprising 93 of 120 (78%) of the original TTF allocated group, versus 117 of 117 (100%) of the original chemotherapy allocated group. This exercise revealed median OS of 7.7 months in the TTF modified ITT (mITT) group compared with 5.9 months in the chemotherapy group (HR=0.69; 95% CI, 0.52 to 0.91; p=0.009). They also showed a trend relationship between proportion of patients with higher TTF compliance and median OS rates (p=0.039). The investigators suggest that TTF provides an OS benefit if used as intended in the FDA-approved label when compared with best chemotherapy. This post hoc analysis is limited as it was not prespecified in the study, includes only 78% of the original TTF allocated patients, and fails to control for noncompliance due to faster clinical deterioration of TTF recipients leading to treatment cessation.

A study published in late 2014 included OS data from 457 patients included in the Patient Registry Dataset (PRiDe), a postmarketing registry of all recurrent GBM patients who received NovoTTF therapy in a real-world, clinical practice setting in 91 centers in the United States between October 2011 and November 2013 (Mrugala, 2014). The median OS rate in the PRiDe clinical practice dataset was reported as significantly superior to that attained in the TTF EF-11 pivotal trial (9.6 months vs 6.6 months; HR=0.66, 95% CI, 0.05 to 0.86; p<0.001). One- and 2-year OS rates for TTF in PRiDe were significantly longer than those in the TTF group in the EF-11 trial (44% vs 20% at 1 year; 30% vs 9% at 2 years, respectively). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

The National Comprehensive Cancer Network Central Nervous System Tumors guidelines (v.1.2015) (NCCN, 2015) has updated the recommendation for the treatment of recurrence of glioblastoma, with the option “consider alternating electric field therapy for glioblastomas” from a category 3 recommendation to a 2B recommendation.

### 2016 Update

A literature search conducted through July 2016 did not reveal any new information that would prompt a change in the coverage statement. The key identified literature is summarized below.

#### **TTF as an Adjunct to Standard Maintenance Care for GBM**

In 2015, Stupp et al published a planned interim analysis of a multicenter, open-label RCT that evaluated maintenance therapy with TTF for GBM (Stupp, 2015). This study enrolled patients with GBM who had completed standard treatment consisting of chemoradiotherapy, plus surgery if indicated. Patients were



randomized in a 2:1 fashion to receive either TTF plus temozolomide (vs temozolomide alone). At the time of the interim analysis, there were 210 patients randomized to TTF plus temozolomide and 105 patients randomized to temozolomide alone. The primary outcome was PFS analyzed by intention-to-treat; a secondary outcome was OS analyzed by per-protocol analysis.

Patients in the TTF group received continuous TTF delivered mainly in the home setting. Patients were trained on use of the device including changing the electrodes, and then treatment continued at home. Patients were encouraged to wear the device continuously, with the exception of short breaks to attend to personal needs. All patients were seen monthly for follow-up. MRI was performed every 2 months and QOL measures administered every 3 months. Tumor progression was adjudicated by a central review committee blinded to treatment group.

Planned interim analysis was performed at a median follow-up of 38 months (range, 18-60 months). Median PFS and median OS are summarized as:

Group Tumor Treatment Fields (TTF) + temozolomide; N= 210 (196 included in per-protocol analysis; progression-free survival (95% confidence interval); hazard ratio (98.7% confidence interval); overall survival (95% confidence interval);p hazard ratio

There were a total of 35 (11%) dropouts during the study, 14 (6.7%) of 210 patients in the TTF group and 21 (20%) of 105 in the temozolomide alone group. Adherence to treatment was defined as wearing the device for at least 18 hours a day, and 157 (75%) of 210 patients met this criteria for adherence. The number of cycles of treatment with temozolomide differed between groups. The TTF group received a median of 6 cycles compared with a median of 4 cycles for the temozolomide alone group. The most common side effect of treatment was local skin irritation, which occurred in 43% of patients treated with TTF.

## 2017 Update

A literature search conducted through July 2017 did not reveal any new information that would prompt a change in the coverage statement.

## 2018 Update

Annual policy review completed with a literature search using the MEDLINE database through June 2018. The key identified literature is summarized below.

## TTF THERAPY AS AN ADJUNCT TO STANDARD MAINTENANCE CARE FOR NEWLY DIAGNOSED GBM

### Randomized Controlled Trials

Stupp et al published results of the EF-14 multicenter, open-label phase 3 RCT that evaluated maintenance therapy with TTF for newly diagnosed GBM (Stupp, 2017). The trial included 695 patients from 83 sites who had supratentorial GBM and had completed standard treatment consisting of biopsy or surgical resection followed by radiotherapy and chemotherapy. A Karnofsky Performance Status (KPS) score of 70 or higher was an additional inclusion criterion to ensure independence in activities of daily living, and patients with rapidly progressing GBM following radiochemotherapy were excluded from the trial. Patients were randomized in a 2:1 fashion to TTF plus maintenance temozolomide or maintenance temozolomide alone.

All patients were seen monthly for follow-up. Quality of life (QOL) was assessed every 3 months, and magnetic resonance imaging (MRI) was performed every 2 months until tumor progression. Tumor progression on MRI was adjudicated by a central review committee blinded to treatment group. The primary outcome was progression-free survival (PFS), and the secondary outcome was overall survival (OS). The analysis was by intention-to-treat, including 26 patients from the control arm who crossed over to TTF following the planned interim analysis.

In 2014, an independent data and safety monitoring board concluded from the planned interim analysis that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended trial termination. The Food and Drug Administration approved the trial termination, and the trial was closed to recruitment with 695 of the planned 700 participants randomized. Control arm participants were allowed to cross over to the experimental treatment at this time. Stupp et al published the interim analysis, which the Food and Drug Administration considered for the 2015 expanded approval of Optune (Stupp, 2015). At the time of the interim analysis, data were available for 210 patients randomized to TTF plus temozolomide and 105 patients to temozolomide alone. Follow-up of the remainder of the 695 enrolled patients continued after enrollment was closed.



Results of the final analysis of the EF-14 trial were similar to the interim analysis. Both PFS and OS improved with the addition of TTF therapy to standard maintenance chemotherapy (ie, temozolomide). PFS increased by 2.7 mo ( $p<0.001$ ) and OS increased by 4.9 mo ( $p<0.001$ ) in the TTF group. The time to a decrease in mental function was 2.5 months longer with TTF therapy ( $p<0.01$ ).

There was a similar percentage of dropouts at the final analysis with 49 (11%) patients in the TTF group and 27 (12%) patients in the temozolomide alone group. More treatment cycles with temozolomide were administered in the TTF group (median, 6 for TTF group vs 5 for controls), a finding that is consistent with the longer PFS. Rates of adverse events were similar between the groups, including rates of seizures. In secondary analysis of patients who had not progressed, there was no reduction in health-related quality of life with TTF compared with temozolomide alone aside from "itchy skin" (Taphoorn, 2018). Interpretation of this result is limited by the low percentage of patients who completed the health-related quality of life assessments at follow-up (65.8% of the 655 patients alive at 3 months and 41.7% of the 473 patients alive at 12 months). A mixed-model analysis, which accounts for missing data, confirmed the results of the mean change from baseline analysis.

The major limitation of this trial is the lack of patient blinding to treatment assignment. However, PFS was assessed by investigators who were blinded to treatment and placebo effects on OS were expected to be minimal. Investigators considered it practically unfeasible (due to the heat and current of the TTF therapy) and ethically unacceptable to submit the control patients to repeated shaving of the head and continuous wear of a sham device over many months.

In summary, the final analysis of the EF-14 trial, which included 695 patients from 83 sites, found a statistically and clinically significant increase of 2.7 months in PFS and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. There was no sham control, and patients were not blinded to treatment assignment, but PFS was assessed by blinded evaluators, and placebo effects on the objective measure of OS were likely to be minimal. There was no evidence of a negative impact of TTF therapy on health-related quality of life, except for itchy skin from the transducers.

**TTF THERAPY AS AN ADJUNCT OR ALTERNATIVE TO MEDICAL THERAPY FOR PROGRESSIVE OR RECURRENT GBM**

Results of a phase 3 multinational RCT (EF-11) published by Stupp et al, was the basis for the 2011 Food and Drug Administration approval of the NovoTTF-100A System (now called Optune) (Stupp, 2012). This trial compared TTF therapy alone with physician's choice medical therapy in 237 adults who had relapsed or progressive glioblastoma. Patients had failed conventional treatment with radiotherapy, chemotherapy, and/or surgery, and more than 80% of participants had failed 2 or more prior chemotherapy regimens. In this trial, the term chemotherapy also applied to targeted agents such as bevacizumab. Patient characteristics and performance of additional post-recurrence debulking surgery were similar in the 2 groups.

Participants were followed monthly, including laboratory tests. MRI images were evaluated at 2, 4, and 6 months from initiation of treatment, with subsequent MRIs performed according to local practice until disease progression. QOL questionnaires were completed every 3 months. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess mortality rates. The primary end point was OS. Secondary end points included PFS, the percentage of patients with PFS at 6 months, time to progression, 1-year survival rate, QOL, and radiologic response. All end points were evaluated using intention-to-treat analysis.

The trial did not reach its primary end point of improved survival compared with active medical therapy. With a median follow-up of 39 months, 93% of patients had died. There was not a statistically significant difference in survival rates at 1, 2, and 3 years between groups. Patients in the TTF group did not, however, suffer the typical systemic side effects of chemotherapy. The most common adverse event in the TTF group was grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids and did not require treatment breaks. Control participants experienced grade 2, 3, or 4 events by organ system related to the pharmacologic activity of chemotherapy agents used. Hematologic events of grade 2 or greater were observed in 17% of chemotherapy patients compared with 3% of TTF patients. Gastrointestinal disorders of grade 2 or greater were identified in 17% of chemotherapy patients compared with 4% of TTF patients. Severe (grades 3-4) hematologic and gastrointestinal toxicity was observed in 7% of chemotherapy controls compared with 1% of the TTF group.



Longitudinal QOL data, available in 63 (27%) participants, showed no meaningful differences between groups for the domains of global health and social functioning. However, cognitive and emotional functioning domains favored TTF therapy. Symptom scale analysis was by treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.

The trial had a number of limitations that included lack of blinding and high loss to follow-up. Discontinuation of TTF therapy occurred in 22% of patients due to noncompliance or inability to handle the device, usually within the first few days. In the control group, 21 (18%) patients did not return to the treatment site, and details on disease progression and toxicity were not available. Longitudinal QOL could be analyzed only for 27% of patients who remained on study therapy for 3 months. The trial was designed as a superiority trial and did not provide adequate evidence of noninferiority.

**Nonrandomized Comparative Studies**

Kesari et al conducted a post hoc analysis of the EF-14 trial to evaluate the efficacy of TTF in patients who had the first recurrence (Kesari, 2017). Some patients in the temozolomide alone group crossed over to receive TTF plus chemotherapy after the first recurrence, resulting in 144 patients who received TTF fields plus chemotherapy and 60 patients who received chemotherapy alone for recurrent GBM. Patient characteristics and second-line treatments were well-balanced between the groups, with bevacizumab the most common second-line therapy. The median OS in patients treated with systemic therapy alone was 9.2 months. In comparison, the group of patients who received TTF therapy in addition to systemic therapy had a median OS of 11.8 months (p=0.043).

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<b>CPT/HCPCS:</b>	A4555 Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
	A9900 Miscellaneous DME supply, accessory, and/or service component of another HCPCS code
	E0766 Electrical stimulation device used for cancer treatment, includes all accessories, any type
	E1399 Durable medical equipment, miscellaneous

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**Group specific policy will supersede this policy when applicable. This policy does not apply to the Wal-Mart Associates Group Health Plan participants or to the Tyson Group Health Plan participants.  
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## Subject: Tumor Treatment Fields Therapy for Glioblastoma

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### DESCRIPTION:

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults. They comprise approximately 15% of all brain and central nervous system tumors and more than 50% of all tumors that arise from glial cells. The peak incidence for GBM occurs between the ages of 45 and 70 years. GBMs are grade IV astrocytomas, and are often resistant to standard chemotherapy.

The primary treatment for GBM is debulking surgery to remove as much of the tumor as possible. At that time, some individuals may undergo implantation of the tumor cavity with a carmustine (bischloroethylnitrosourea [BCNU])–impregnated wafer. Depending on the individual’s physical condition, adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of the 2 are sometimes given. After adjuvant therapy, some may undergo maintenance therapy with temozolomide.

No standard treatment exists for recurrent GBM. In those with disease that recurs after these initial therapies, additional debulking surgery may be used if recurrence is localized. Other treatment options for recurrent disease include various forms of systemic medications such as bevacizumab, bevacizumab plus chemotherapy (eg, irinotecan, BCNU/chloroethylnitrosourea [CCNU], temozolomide), temozolomide, nitrosourea, PCV (procarbazine, CCNU, vincristine), cyclophosphamide, and platinum-based agents. External beam radiotherapy (EBRT) also may be used to treat recurrent GBM. Response rates in recurrent disease are less than 10%, and progression-free survival rates at 6 months are less than 20%.



TTF therapy is a noninvasive technology that is intended to treat GBM on an outpatient basis using electrical fields. TTF therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis. TTF are proposed to inhibit rapidly dividing tumor cells by 2 mechanisms, arrest of cell proliferation and destruction of cells while undergoing division.

TTF therapy via the Optune™ (formerly NovoTTF-100A System) System is delivered by a battery-powered, portable device that generates the fields via disposable electrodes that are noninvasively attached to the individual's shaved scalp over the site of the tumor. The device is used by the individual at home on a continuous basis for the duration of treatment, which can last for several months. The device is carried in a backpack or shoulder pack while carrying out activities of daily living.

Treatment planning software (eg, NovoTAL) is available and designed to be utilized prior to starting TTF treatment. NovoTAL is optional software that a physician can purchase and use to create individualized treatment maps. It is purported to allow the physician to individualize treatment by determining optimal placement of the transducer arrays, based on the individual's most recent magnetic resonance imaging (MRI) scan, head size and tumor location. It is performed in-office. Physicians are required to complete training and certification in order to use the NovoTAL System. The Optune™ device is available preset from Novocure. The device is preset to deliver TTF at a frequency of 200 kHz and is operated by the patient independently. It is monitored periodically by device specialists, who are available 24/7 to provide technical support to the patient, their family and physician.

## REGULATORY STATUS

The Optune™ (formerly NovoTTF-100A System) System was approved by the FDA in April 2011, as a stand-alone treatment for adults age 22 years or older with confirmed GBM that recurs or progresses after surgical and radiation options have been exhausted. On October 5, 2015 the FDA granted approval for use of Optune™ in combination with temozolomide to treat adults age 22 years or older with newly diagnosed, supratentorial GBM after maximal debulking surgery and completion of radiation therapy, together with concomitant standard of care chemotherapy.

## POSITION STATEMENT:

The use of tumor treatment fields therapy (TTF) to treat glioblastoma **meets the definition of medical necessity** when **ALL** of the following criteria are met:

- The device is FDA approved
- Age 22 or older
- There is histologically-confirmed supratentorial glioblastoma (also known as glioblastoma multiforme [GBM] or World Health Organization [WHO] grade IV astrocytoma)
- Initial treatment with debulking surgery or biopsy followed by chemoradiation with concomitant temozolomide and radiotherapy has been completed, with no documented tumor progression\*
- TTF is used in combination with temozolomide



- Karnofsky Performance Status score of 70 or higher, OR Eastern Cooperative Oncology Group (ECOG) performance status 0-1

\* Progression is defined as tumor growth greater than 25% compared to smallest measured tumor area, or the appearance of one or more new GBM lesions in the brain.

The use of tumor treatment fields therapy (TTF) to treat glioblastoma recurrence **meets the definition of medical necessity** when **ALL** of the following criteria are met:

- The device is FDA approved
- Age 22 or older
- There is histologically-confirmed recurrence of supratentorial glioblastoma (also known as glioblastoma multiforme [GBM] or World Health Organization [WHO] grade IV astrocytoma) following treatment with chemotherapy and/or radiation
- TTF is used as monotherapy

The use of tumor treatment fields therapy (TTF) for all other indications is considered **experimental or investigational**. There is insufficient clinical evidence in the peer-reviewed literature on this technology to support its safety, effectiveness, and long term effects on net health outcomes for other types of cancer.

The use of treatment planning software (eg, NovoTAL) for use with tumor treatment fields for any indication is considered **experimental or investigational**. Data in published medical literature are inadequate to permit scientific conclusions on long-term and net health outcomes.

## **BILLING/CODING INFORMATION:**

### **HCPCS Coding**

A4555	Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only
E0766	Electrical stimulation device, used for cancer treatment, includes all accessories, any type

## **REIMBURSEMENT INFORMATION:**

Refer to section entitled [\*\*POSITION STATEMENT\*\*](#).

## **PROGRAM EXCEPTIONS:**

**Federal Employee Program (FEP):** Follow FEP guidelines.

**State Account Organization (SAO):** Follow SAO guidelines.

**Medicare Advantage products:** The following Durable Medical Equipment Regional Carrier (DMERC) Local Coverage Determination (LCD) was reviewed on the last guideline reviewed date: Tumor Treatment Field Therapy (TTFT) (L34823), located at [cgsmedicare.com](https://www.cms.gov/medicare/coverage/determinations/lcds/l34823)



## DEFINITIONS:

<b>Eastern Cooperative Oncology Group (ECOG) Performance Status:</b>	
A scale used to determine an individual's level of functioning:	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

<b>Karnofsky Performance Status Score:</b>	
A scale used by healthcare providers to quickly evaluate how an individual is feeling on any given day:	
100	Normal, no complaints
90	Able to carry on normal activities. Minor signs or symptoms of disease
80	Normal activity with effort
70	Care for self. Unable to carry on normal activity or to do active work
60	Requires occasional assistance, but able to care for most of his needs
50	Requires considerable assistance and frequent medical care
40	Disabled. Requires special care and assistance



30	Severly disabled. Hospitalisation indicated though death nonimminent
20	Very sick. Hospitalisation necessary. Active supportive treatment necessary
10	Moribund
0	Dead

### RELATED GUIDELINES:

None applicable.

### OTHER:

None applicable.

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### **COMMITTEE APPROVAL:**

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy & Coverage Committee on 04/26/18.

### **GUIDELINE UPDATE INFORMATION:**

10/15/15	New Medical Coverage Guideline.
04/15/17	Scheduled review. Revised Description section. Added coverage criteria for TTF therapy. Revised Program Exceptions section and Definitions section. Updated references.
05/15/18	Scheduled review. Added coverage statement (E/I) for treatment planning software (eg, NovoTAL). Updated references.



## Medical Policy



An independent licensee of the  
Blue Cross Blue Shield Association

### Title: Tumor Treating Fields Therapy

#### **Professional**

Original Effective Date: August 1, 2018

Revision Date(s): August 1, 2018

Current Effective Date: August 1, 2018

#### **Institutional**

Original Effective Date: August 1, 2018

Revision Date(s): August 1, 2018

Current Effective Date: August 1, 2018

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Populations	Interventions	Comparators	Outcomes
Individuals: • With newly diagnosed glioblastoma multiforme on maintenance therapy after initial treatment	Interventions of interest are: • Tumor treating fields therapy as an adjunct to standard maintenance therapy	Comparators of interest are: • Standard maintenance therapy alone	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity
Individuals: • With progressive or recurrent glioblastoma multiforme	Interventions of interest are: • Tumor treating fields therapy as an adjunct or alternative to medical therapy	Comparators of interest are: • Standard medical therapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity



**DESCRIPTION**

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

**OBJECTIVE**

The objective of this policy is to determine whether the use of tumor treating fields therapy improves the net health outcome for patients with solid tumors including glioblastoma multiforme.

**BACKGROUND****Glioblastoma Multiforme**

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.<sup>1</sup> GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (eg, bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors.<sup>1</sup> The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to 1 year, and the 5-year survival rate was around 5%.<sup>2</sup>

Clinical Context and Therapy Purpose

The purpose of alternating electrical field therapy, more commonly known as tumor treating fields (TTF) therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

Treatment of Newly Diagnosed GBM

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these 2 therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival rates with temozolomide are higher in patients who have O<sup>6</sup>-methylguanine-DNA methyltransferase (*MGMT*) gene promoter methylation.



Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice (see the Supplemental Information section).<sup>3</sup> For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially all patients.

#### Treatment of Recurrent GBM

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (eg, lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%.<sup>4</sup> There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

The questions addressed in this evidence review are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

#### Patients

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.



### Interventions

TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields.<sup>4-6</sup> TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. TTF therapy is proposed to inhibit tumor growth by 2 mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase.<sup>5,6</sup> Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune (formerly NovoTTF-100A System) is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to **the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved** and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

### Comparators

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

The following practices are currently being used to make decisions about recurrent GBM: medical therapy.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months.<sup>4</sup>

### Outcomes

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

### Timing

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.



Setting

The setting is outpatient care by an oncologist or neuro-oncologist.

**REGULATORY STATUS**

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.<sup>7</sup> The FDA-approved label reads as follows: **"The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."**

In September 2014, FDA approved Novocure's request for a product name change from NovoTTF-110A System to Optune®.<sup>8</sup>

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.<sup>9</sup> The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: **"This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."**

FDA product code: NZK.



**POLICY**

- A. Tumor treating fields therapy to treat glioblastoma multiforme is considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:
1. **Adult patients  $\geq 18$  years** of age
  2. Supratentorial tumor
  3. **Karnofsky Performance Status score  $\geq 70\%$**
  4. Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (see Policy Guidelines).
- B. Tumor treating fields therapy is considered **experimental / investigational** in all other conditions, including but not limited to, the following situations:
1. As an adjunct to standard medical therapy (eg, bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
  2. As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
  3. For brain metastases
  4. For cancer in areas other than the brain.

**Policy Guidelines**

1. Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth  $>25\%$  compared with the smallest tumor area measured in the patient during the trial or appearance of 1 or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).
2. The Food and Drug Administration label includes the following notices:
  - a. Patients should use Optune for at least 18 hours a day to get the best response to treatment
  - b. Patients should finish at least 4 full weeks of therapy to get the best response to treatment. Stopping treatment before 4 weeks lowers the chances of a response to treatment.



## **RATIONALE**

The literature update was performed through April 5, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

For this review, 3 indications are evaluated: (1) tumor treating fields (TTF) as an adjunct to maintenance chemotherapy in newly diagnosed patients following initial treatment with surgery, radiotherapy and chemotherapy and (2) TTF as an adjunct or (3) alternative to medical therapy (eg, bevacizumab, chemotherapy) in progressive or recurrent glioblastoma multiforme (GBM).

### **Study Selection**

The PICOTS was used to select relevant studies.

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Within each category of study design, studies with larger sample size studies and longer duration were sought.

### **TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM** **Randomized Controlled Trials**

Stupp et al (2017) published results of the EF-14 multicenter, open-label phase 3 RCT that evaluated maintenance therapy with TTF for newly diagnosed GBM.<sup>10</sup> The trial included 695 patients from 83 sites who had supratentorial GBM and had completed standard treatment consisting of biopsy or surgical resection followed by radiotherapy and chemotherapy (see Table 1). A Karnofsky Performance Status (KPS) score of 70 or higher was an additional inclusion criterion to ensure independence in activities of daily living, and patients with rapidly progressing GBM following radiochemotherapy were excluded from the trial. Patients were randomized in a 2:1 fashion to TTF plus maintenance temozolomide or maintenance temozolomide alone.



All patients were seen monthly for follow-up. Quality of life (QOL) was assessed every 3 months, and magnetic resonance imaging (MRI) was performed every 2 months until tumor progression. Tumor progression on MRI was adjudicated by a central review committee blinded to treatment group. The primary outcome was progression-free survival (PFS), and the secondary outcome was overall survival (OS). The analysis was by intention-to-treat, including 26 patients from the control arm who crossed over to TTF following the planned interim analysis.

In 2014, an independent data and safety monitoring board concluded from the planned interim analysis that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended trial termination. The Food and Drug Administration approved the trial termination, and the trial was closed to recruitment with 695 of the planned 700 participants randomized. Control arm participants were allowed to cross over to the experimental treatment at this time. The interim analysis, which the Food and Drug Administration considered for the 2015 expanded approval of Optune, was published by Stupp et al (2015).<sup>11</sup> At the time of the interim analysis, data were available for 210 patients randomized to TTF plus temozolomide and 105 patients to temozolomide alone. Follow-up of the remainder of the 695 enrolled patients continued after enrollment was closed.

**Table 1.** Key Randomized Controlled Trial Characteristics for Newly Diagnosed Glioblastoma

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Stupp et al (2017) <sup>10</sup> ; EF-14	U.S., E.U., South Korea, Israel	83	2009-2016	695 newly diagnosed with GBM and treated by radiochemotherapy <b>KPS score ≥70</b>	TTF >18 h/d plus maintenance temozolomide (n=466)	Maintenance temozolomide alone (5 d every 28 d for 6 cycles) (n=229)

GBM: glioblastoma multiforme; h/d: hours per day; KPS: Karnofsky Performance Status; TTF: tumor treatment fields.

Results of the final analysis of the EF-14 trial were similar to the interim analysis and are shown in Table 2. Both PFS and OS improved with the addition of TTF therapy to standard maintenance chemotherapy (ie, temozolomide). PFS increased by 2.7 mo ( $p<0.001$ ) and OS increased by 4.9 mo ( $p<0.001$ ) in the TTF group. The time to a decrease in mental function was 2.5 months longer with TTF therapy ( $p<0.01$ ).

There was a similar percentage of dropouts at the final analysis—with 49 (11%) patients in the TTF group and 27 (12%) patients in the temozolomide alone group. More treatment cycles with temozolomide were administered in the TTF group (median, 6 for TTF group vs 5 for controls), a finding that is consistent with the longer PFS. Rates of adverse events were similar between the groups, including rates of seizures. In secondary analysis of patients who had not progressed, there was no reduction in health-related quality of life with TTF compared with temozolomide **alone aside from “itchy skin”**.<sup>12</sup> Interpretation of this result is limited by the low percentage of patients who completed the health-related quality of life assessments at follow-up (65.8% of the 655 patients alive at 3 months and 41.7% of the 473 patients alive at 12 months). A mixed-model analysis, which accounts for missing data, confirmed the results of the mean change from baseline analysis.



**Table 2.** Key Randomized Controlled Trial Results for Newly Diagnosed Glioblastoma

Study	Final N (%)	Median PFS (95% CI), mo	Median OS (95% CI), mo	Systemic Adverse Events, n (%)	Seizures, n (%)	Time to 6-Point Decline in MMSE Score (95% CI), mo
Stupp et al (2017) <sup>10</sup>						
TTF + temozolomide	417 (89)	6.7 (6.1 to 8.1)	20.9 (19.3 to 22.7)	218 (48)	26 (6)	16.7 (14.7 to 19.0)
Temozolomide alone	202 (88)	4.0 (3.8 to 4.4)	16.0 (14.0 to 18.4)	94 (44)	13 (6)	14.2 (12.7 to 17.0)
HR (95% CI)		0.63 (0.52 to 0.76)	0.63 (0.53 to 0.76)			0.79 (0.66 to 0.95)
P value		<0.001	<0.001	0.58		0.01

CI: confidence interval; HR: hazard ratio; MMSE: Mini-Mental State Examination; OS: overall survival; PFS: progression-free survival; TTF: tumor treatment fields.

Tables 3 and 4 display notable gaps identified in this trial, the major limitation is the lack of patient blinding to treatment assignment. However, PFS was assessed by investigators who were blinded to treatment and placebo effects on OS were expected to be minimal. Investigators considered it practically unfeasible (due to the heat and current of the TTF therapy) and ethically unacceptable to submit the control patients to repeated shaving of the head and continuous wear of a sham device over many months.

**Table 3.** Relevance Gaps

Study; Trial	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcome <sup>d</sup>	Follow-Up <sup>e</sup>
Stupp et al (2017) <sup>10</sup> ; EF-14			3. Possible differences in post-progression treatment affecting overall survival		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 4.** Study Design and Conduct Gaps

Study; Trial	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
Stupp et al (2017) <sup>10</sup> ; EF-14		1. No sham control and not blinded to treatment assignment				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).



<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

### Section Summary: TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM

The final analysis of the EF-14 trial, which included 695 patients from 83 sites, found a statistically and clinically significant increase of 2.7 months in PFS and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. There was no sham control, and patients were not blinded to treatment assignment, but PFS was assessed by blinded evaluators, and placebo effects on the objective measure of OS were likely to be minimal. There was no evidence of a negative impact of TTF therapy on health-related quality of life, except for itchy skin from the transducers.

### **TTF Therapy as an Adjunct or Alternative to Medical Therapy for Progressive or Recurrent GBM**

#### Randomized Controlled Trials

The 2011 Food and Drug Administration approval of the NovoTTF-100A System (now called Optune) was based on a phase 3 multinational RCT (EF-11), results of which were published by Stupp et al (2012).<sup>4</sup> **This trial compared TTF therapy alone with physician's choice medical therapy** in 237 adults who had relapsed or progressive glioblastoma (see Table 5). Patients had failed conventional treatment with radiotherapy, chemotherapy, and/or surgery, and more than 80% of participants had failed 2 or more prior chemotherapy regimens. In this trial, the term chemotherapy also applied to targeted agents such as bevacizumab. Patient characteristics and performance of additional post-recurrence debulking surgery were similar in the 2 groups.

**Table 5.** Summary of Key Randomized Controlled Trial Characteristics for Progressive or Recurrent Glioblastoma

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Stupp et al (2012) <sup>4</sup> ; EF-11	U.S., E.U., Israel	28	1987-2013	237 adults with relapsed or progressive supratentorial glioblastoma KPS score $\geq 70\%$	120 patients treated with TTF alone, 93 (78%) completed 1 cycle	117 patients treated with physician's choice of medical therapy <sup>a</sup>

EU: European Union; KPS: Karnofsky Performance Status; TTF: tumor treating fields.

<sup>a</sup> Medical therapy included bevacizumab, irinotecan, nitrosoureas, platinum-based chemotherapy (ie, carboplatin); temozolomide; or a combination of procarbazine, chloroethyl ether, and vincristine.

Participants were followed monthly, including laboratory tests. MRI images were evaluated at 2, 4, and 6 months from initiation of treatment, with subsequent MRIs performed according to local practice until disease progression. QOL questionnaires were completed every 3 months. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess mortality rates. The primary end point was OS. Secondary end points included PFS, the percentage of patients with PFS at 6 months, time to progression, 1-year survival rate, QOL, and radiologic response. All end points were evaluated using intention-to-treat analysis.

The trial did not reach its primary end point of improved survival compared with active medical therapy (see Table 6). With a median follow-up of 39 months, 93% of patients had died. There



was not a statistically significant difference in survival rates at 1, 2, and 3 years between groups. Patients in the TTF group did not, however, suffer the typical systemic side effects of chemotherapy. The most common adverse event in the TTF group was grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids and did not require treatment breaks. Control participants experienced grade 2, 3, or 4 events by organ system related to the pharmacologic activity of chemotherapy agents used. Hematologic events of grade 2 or greater were observed in 17% of chemotherapy patients compared with 3% of TTF patients. Gastrointestinal disorders of grade 2 or greater were identified in 17% of chemotherapy patients compared with 4% of TTF patients. Severe (grades 3-4) hematologic and gastrointestinal toxicity was observed in 7% of chemotherapy controls compared with 1% of the TTF group.

Longitudinal QOL data, available in 63 (27%) participants, showed no meaningful differences between groups for the domains of global health and social functioning. However, cognitive and emotional functioning domains favored TTF therapy. Symptom scale analysis by treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.

The trial had a number of limitations (see Tables 7 and 8), that included lack of blinding and high loss to follow-up. Discontinuation of TTF therapy occurred in 22% of patients due to noncompliance or inability to handle the device, usually within the first few days. In the control group, 21 (18%) patients did not return to the treatment site, and details on disease progression and toxicity were not available. Longitudinal QOL could be analyzed only for 27% of patients who remained on study therapy for 3 months. The trial was designed as a superiority trial and did not provide adequate evidence of noninferiority.

**Table 6.** Summary of Key Randomized Controlled Trial Results for Recurrent or Progressive Glioblastoma

Study; Trial	LTFU, n (%)	Median OS, mo	Progression-Free Survival		Overall Survival (95% CI), %		
			Median, mo	Rate at 6 Months (95% CI), %	1 Year	2 Years	3 Years
Stupp et al (2012) <sup>4</sup> ; EF-11							
TTF	23 (22)	6.6	2.2	21.4 (13.5 to 29.3)	20	8 (4 to 13)	4 (1 to 8)
PCC	12 (18)	6.0	2.1	15.1 (7.8 to 22.3)	20	5 (3 to 10)	1 (0 to 3)
HR (95% CI)		0.86 (0.66 to 1.12)	0.81 (0.60 to 1.09)				
P value		0.27	0.16	0.13			

CI: confidence interval; HR: hazard ratio; LTFU: loss to follow-up; PCC: physician's choice chemotherapy; TTF: tumor treating fields.

**Table 7.** Relevance Gaps

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Stupp et al (2012) <sup>4</sup> ; EF-11			2. Physician's choice chemotherapy		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.



<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 8.** Study Design and Conduct Gaps

Study; Trial	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>d</sup>	Data Completeness <sup>e</sup>	Power <sup>d</sup>	Statistical <sup>f</sup>
Stupp et al (2012) <sup>4</sup> ; EF-11		1. Not blinded to treatment assignment		1. 78% of TTF group completed only 1 cycle of therapy, 18% of control group lost to follow-up 1. Longitudinal QOL data were available for 27% of patients		1. Not designed as a noninferiority trial

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. QOL: quality of life.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

### Nonrandomized Comparative Studies

Kesari et al (2017) conducted a post hoc analysis of the EF-14 trial (see Stupp et al [2017] above) to evaluate the efficacy of TTF in patients who had the first recurrence.<sup>13</sup> Some patients in the temozolomide alone group crossed over to receive TTF plus chemotherapy after the first recurrence, resulting in 144 patients who received TTF fields plus chemotherapy and 60 patients who received chemotherapy alone for recurrent GBM (see Table 9). Patient characteristics and second-line treatments were well-balanced between the groups, with bevacizumab the most common second-line therapy. The median OS in patients treated with systemic therapy alone was 9.2 months (see Table 10). In comparison, the group of patients who received TTF therapy in addition to systemic therapy had a median OS of 11.8 months ( $p=0.043$ ).

A registry study published Mrugala et al (2014) assessed OS data from patients who received NovoTTF therapy in a real-world, clinical practice setting (see Table 9).<sup>14</sup> Concurrent treatment was not captured in the registry, and it is possible that some patients received combination therapy. Median OS in the PRiDe clinical practice dataset (9.6 mo) was reported as superior to that attained in the EF-11 pivotal trial (6.6 mo,  $p<0.001$ ) (see Table 10). More patients in the PRiDe registry were treated for first recurrence (33% vs 9%), and more had received bevacizumab as prior therapy (55% vs 19%). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.



**Table 9.** Characteristics of Key Nonrandomized Trial Results

Study	Study Type	Country	Dates	Participants	TTF	Controls	FU
Kesari et al (2017) <sup>13</sup>	EF-14 post hoc analysis	U.S., E.U., South Korea, Israel	2009-2016	204 patients with first recurrence in the EF-14 trial	144 patients treated with TTF plus second-line chemotherapy	60 patients treated with second-line chemotherapy	12.6 mo
Mrugala et al (2014) <sup>14</sup>	Registry	U.S. (91 centers)	2011-2013	457 patients with recurrent GBM	Patient Registry Dataset (PRiDe)	EF-11	

FU: follow-up; GBM: glioblastoma; TTF: tumor treating fields.

**Table 10.** Summary of Key Nonrandomized Trial Results

Study	Median OS, mo	Median OS With Bevacizumab, mo
Kesari et al (2017) <sup>13</sup> ; EF-14		
TTF plus chemotherapy	11.8	11.8
Chemotherapy alone	9.2	9.0
Hazard ratio (95% CI)	0.70 (0.48 to 1.00)	0.61 (0.37 to 0.99)
P value	0.049	0.043
		1-Year OS, %
		2-Year OS, %
Mrugala et al (2014) <sup>14</sup>		
PRiDe Registry	9.6	44
EF-11	6.6	20
Hazard ratio (95% CI)	0.66 (0.05 to 0.86)	30
P value	<0.001	9

CI: confidence interval; OS: overall survival; TTF: tumor treating fields.

Post hoc analyses of the EF-11 pivotal trial have been reported. Wong et al (2014) published a subgroup analysis to determine characteristics of responders and nonresponders in the active treatment and active treatment control.<sup>15</sup> They found that responders had a lower grade of histology and lower daily dexamethasone use than nonresponders. A second post hoc analysis by Kanner et al (2014) of the EF-11 pivotal trial data was performed to evaluate OS among patients who finished at least 1 complete course of TTF or chemotherapy.<sup>16</sup> The investigators reported that median OS was 7.7 months in the TTF group compared with 5.9 months in the chemotherapy group ( $p=0.009$ ). These post hoc analyses are considered to be hypothesis-generating.

#### *Section Summary: TTF Therapy as an Adjunct or Alternative to Chemotherapy for Progressive or Recurrent GBM*

The single RCT for TTF as an alternative to chemotherapy reported that outcomes following TTF therapy were similar to outcomes following standard chemotherapy. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. The noninferiority of TTF compared with chemotherapy might be considered a sufficient health benefit, if TTF reduced treatment toxicity. However, because the trial was not designed as a noninferiority trial no inferences of **noninferiority compared with chemotherapy can be made. Physician's choice therapy during the** trial was heterogenous, although analysis indicated that survival was not affected by choice of chemotherapy. More patients in the TTF group than in the control group did not complete the treatment course. The number of patients who contributed QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators might have been subject to bias due to the lack of blinding.



A nonrandomized post hoc evaluation of the EF-14 trial suggests that TTF may improve survival when combined with chemotherapy for recurrent GBM. This analysis should be considered hypothesis-generating, and further study in high-quality RCTs is needed.

### **SUMMARY OF EVIDENCE**

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes an RCT. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with **physicians' choice chemotherapy. Because no serious adverse effects have been identified with** TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

### **CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 3 physician specialty societies (one of which provided 6 responses and 2 of which provided 1 response each) and 1 academic medical center (total of 9 individual responses) while this policy was under review in 2016. There was majority support, but not consensus, for the use of tumor treatment fields therapy as an adjunct to maintenance treatment following initial therapy for glioblastoma multiforme. There was mixed



support for the use of tumor treatment fields as an alternative to chemotherapy in advanced or recurrent glioblastoma multiforme.

### PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2018) include recommendations for the treatment of glioblastoma (see Table 11).<sup>3</sup> For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate O<sup>6</sup>-methylguanine-DNA methyltransferase promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric field therapy is a category 1 recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a category 2B recommendation.

**Table 11.** Guidelines for Adjuvant Treatment of Glioblastoma, by Age and Performance Status

Age, y	KPS Score, %	Treatment Options	Category
≤70	≥60	<ul style="list-style-type: none"> <li>• Standard RT plus concurrent and adjuvant temozolomide plus TTF</li> <li>• Standard RT plus concurrent and adjuvant temozolomide</li> </ul>	1
≤70	<60	<ul style="list-style-type: none"> <li>• Hypofractionated RT with/without concurrent or adjuvant temozolomide</li> <li>• Temozolomide</li> <li>• Palliative/best supportive care</li> </ul>	2A
>70	≥60	<ul style="list-style-type: none"> <li>• Hypofractionated RT plus concurrent and adjuvant temozolomide</li> <li>• Standard RT plus concurrent and adjuvant temozolomide plus TTF</li> <li>• Temozolomide alone</li> <li>• Hypofractionated brain RT alone</li> </ul>	1
>70	<60	<ul style="list-style-type: none"> <li>• Hypofractionated brain RT alone</li> <li>• Temozolomide alone</li> <li>• Palliative/best supportive care</li> </ul>	2A

KPS: Karnofsky Performance Status; RT: radiotherapy; TTF: tumor treating fields.

### U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

### ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 12. Of particular note are the phase 3 trials evaluating TTF therapy in non-small-cell lung cancer and pancreatic cancer. TTF therapy is an active area of research for mechanisms underlying its effects on cancer cells.

**Table 12.** Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01971281 <sup>a</sup>	A Phase II Study of TTFields (150 kHz) Concomitant With Gemcitabine and TTFields Concomitant With Gemcitabine Plus Nab-paclitaxel for Front-line Therapy of Advanced Pancreatic Adenocarcinoma	40	Dec 2017 (ongoing)
NCT01894061 <sup>a</sup>	A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma	40	Dec 2018
NCT02663271 <sup>a</sup>	A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFields and Pulsed	18	Mar 2019



NCT No.	Trial Name	Planned Enrollment	Completion Date
	Bevacizumab Treatment in Patients With Bevacizumab-refractory Recurrent Glioblastoma		
NCT02831959 <sup>a</sup>	Pivotal, Open-label, Randomized Study of Radiosurgery With or Without Tumor Treating Fields (TTFields) (150kHz) for 1-10 Brain Metastases From Non-small Cell Lung Cancer (NSCLC) (METIS)	270	Jul 2019
NCT02973789 <sup>a</sup>	LUNAR: Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields) Concurrent With Standard of Care Therapies for Treatment of Stage 4 Non-small Cell Lung Cancer (NSCLC) Following Platinum Failure	534	Dec 2021
NCT02743078 <sup>a</sup>	Phase II Trial Of Optune® Plus Bevacizumab In Bevacizumab-Refractory Recurrent Glioblastoma	85	Aug 2022
NCT03377491 <sup>a</sup>	EF-27 Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields, 150kHz) Concomitant With Gemcitabine and Nab-paclitaxel for Front-line Treatment of Locally-advanced Pancreatic Adenocarcinoma (PANOV3)	556	Dec 2022

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

## CODING

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

### CPT/HCPCS

A4555	Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only
E0766	Electrical stimulation device, used for cancer treatment, includes all accessories, any type

### ICD-10 Diagnoses

C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles
C71.1	Malignant neoplasm of frontal lobe
C71.2	Malignant neoplasm of temporal lobe
C71.3	Malignant neoplasm of parietal lobe
C71.4	Malignant neoplasm of occipital lobe
C71.5	Malignant neoplasm of cerebral ventricle
C71.6	Malignant neoplasm of cerebellum
C71.7	Malignant neoplasm of brain stem
C71.8	Malignant neoplasm of overlapping sites of brain

## REVISIONS

08-01-2018	Policy added to the bcbsks.com web site on 08-01-2018.
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## Medical Policy



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Joint Medical Policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and is therefore subject to change.

**\*Current Policy Effective Date: 5/1/18**  
(See policy history boxes for previous effective dates)

### Title: Tumor-Treatment Fields Therapy for Glioblastoma

#### Description/Background

Glioblastoma multiforme is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during the course of treatment. Tumor-treatment fields (TTF) therapy is a new, noninvasive technology that is intended to treat glioblastoma using electrical fields.

The Optune device has been approved by the FDA to treat patients with newly-diagnosed glioblastoma multiforme (GBM), an aggressive form of brain cancer. It is given along with the chemotherapy drug temozolomide (TMZ) following standard treatments that include surgery, and a combination of radiation therapy and chemotherapy when used together.

The FDA based its approval of the expanded indication of the Optune device on results from a clinical trial involving 695 patients newly diagnosed with GBM that compared those who used Optune with TMZ to those receiving TMZ alone. Patients who used the device along with TMZ lived, on average, about seven months with no disease progression and survived for an average of 19.4 months after starting treatment. Those who were only treated with TMZ, lived, on average four months with no disease progression and survived for an average of 16.6 months after starting treatment.

In the clinical study used to support the expanded indication, patients treated with the device and TMZ lived on average three months longer than those treated with the drug alone.

#### BACKGROUND

##### Glioblastoma Multiforme

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults, and they comprise approximately 15% of all brain and central nervous system tumors and more than 50% of all tumors that arise from glial cells.(1)



The peak incidence for GBM occurs between the ages of 45 and 70 years. GBMs are grade IV astrocytomas, the most deadly type of glial cell tumor, and are often resistant to standard chemotherapy.(1) According to the National Comprehensive Cancer Network, GBM is the "most lethal brain tumor with only a third of patients surviving for 1 year and less than 5% living beyond 5 years."(2)

### **Treatment of Glioblastoma Multiforme**

The primary treatment for patients newly diagnosed with GBM is to resect the tumor, confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. At that time, some patients may undergo implantation of the tumor cavity with a carmustine (BCNU)-impregnated wafer.(2) Depending on the patient's physical condition, adjuvant radiation therapy, chemotherapy (typically temozolomide), or a combination of the two are sometimes given. After adjuvant therapy, some patients may undergo maintenance therapy with temozolomide. Prognostic factors for success of therapy are age, histology, and performance status or physical condition of the patient.

No standard treatment exists for recurrent GBM. In patients with disease that recurs after initial treatment, additional debulking surgery may be used if recurrence is localized. Other treatment options for recurrent disease include various forms of systemic medications such as bevacizumab, bevacizumab plus chemotherapy (eg, irinotecan, BCNU/chloroethylnitrosourea [CCNU], temozolomide), temozolomide, nitrosourea, PCV (procarbazine, CCNU, vincristine), cyclophosphamide, and platinum-based agents.(2) External beam radiotherapy (EBRT) also may be used to treat recurrent GBM.

Fractionated external-beam radiotherapy after surgery is standard adjuvant therapy and may be used to treat recurrent GBM. Response rates in recurrent disease are less than 10%, and progression-free survival rates at 6 months are less than 20%. (2,3)

### ***Tumor Treatment Field Therapy***

TTF therapy is a new, noninvasive technology that is intended to treat GBM on an outpatient basis using electrical fields. (3-5) TTF therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis. TTF are proposed to inhibit rapidly dividing tumor cells by two mechanisms; arrest of cell proliferation and destruction of cells while undergoing division. (4,5)

Optune, formerly NovoTTF-100A™ System, is the only legally marketed TTF delivery system available in the United States. Optune is a portable device that generates alternating electrical fields within the body (called tumor treatment fields). The fields are conducted via disposable electrode patches that are attached to the patient's shaved scalp, over the site of the tumor. (3,4) The device is used by the patient at home on a continuous basis (20-24 hours per day) for the duration of treatment, which can last for several months. Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living. (6)

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## **Regulatory Status**

The NovoTTF-100A™ System (assigned the generic name of TTF) was approved by FDA in April 2011 through the premarket approval process. (7) The FDA-approved label reads as



follows: “The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed GBM, following histologically or radiologically confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment, and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted.”(7)

In September 2014, FDA approved Novocure’s request to change its product name from NovoTTF-110A System to Optune™. (8)

In October 2015, FDA expanded the indication for Optune™ in combination with temozolomide to include newly diagnosed glioblastoma.(6) The device was granted priority review status in May 2015 because there was no legally marketed alternative device currently available for the treatment of newly diagnosed GBM that represents a life-threatening condition.

Optune was initially approved in 2011, by the FDA, to treat patients with GBM that recurred or progressed after chemotherapy. With the 2015 expanded indication, Optune™ can be used as part of a standard treatment for GBM before the disease progresses. For newly diagnosed GBM, Optune™ is not intended to be used as a substitute for standard treatments, but rather as an adjunct therapy.

For newly diagnosed GBM, Optune™ is given along with the chemotherapy drug temozolomide (TMZ) following standard treatments that include surgery and the combination of radiation and chemotherapy. Optune™ should not be used without a physician’s supervision. Patients should not use Optune™ if they have an active implanted medical device, a skull defect or known sensitivity to conductive hydrogels, such as those used on electrocardiogram stickers. (21)

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## Medical Policy Statement

The safety and effectiveness of tumor-treatment fields (TTF) therapy has been established. It is a useful therapeutic option for patients meeting specific selection criteria.

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## Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

### Inclusions:

Tumor treatment field therapy may be medically necessary when prescribed by a physician for the treatment of newly diagnosed, histologically confirmed supratentorial glioblastoma multiforme in:

- Adults (22 years of age and older) **AND**
- When used as an adjunct therapy to standard treatments that include maximal debulking surgery and completion of radiation together with the chemotherapy drug temozolomide (TMZ)

**OR**



- For adults 22 years of age and older with reoccurrence of histologically or radiologically confirmed supratentorial glioblastoma multiforme, the Tumor Treatment Fields may be used as monotherapy as an alternative to standard medical therapy

### **Exclusions:**

Tumor treatment field therapy is considered investigational/experimental:

- Combined with chemotherapy other than TMZ
- When used for any indications other than those listed above

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**CPT/HCPCS Level II Codes** *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

### **Established codes:**

A4555	E0766	95999
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### **Other codes (investigational, not medically necessary, etc.):**

E1399	A9900	77299
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## **Rationale**

Re-radiation options are limited for glioblastoma (GBM) patients who have received initial external-beam radiotherapy due to radiation tolerances. The tumors are locally invasive but do not metastasize, therefore, tumor treating fields (TTF) therapy as a locoregional intervention is proposed to treat GBM. For this review, 2 indications will be considered: (1) TTF as an alternative to chemotherapy in progressive or recurrent GBM and (2) TTF as an adjunct to maintenance treatment in patients following initial treatment. Comparative trials are essential to determine efficacy in this area, and randomized controlled trials (RCTs) are needed to control for heterogeneity in the patient populations and other confounders of outcome. This review will include both RCTs and nonrandomized comparative trials.

## **TTF AS AN ALTERNATIVE TO CHEMOTHERAPY FOR PROGRESSIVE OR RECURRENT GBM**

### **Randomized Controlled Trials**

The U.S. Food and Drug Administration (FDA) approval of the NovoTTF-100A system was based on a phase 3, multinational prospective randomized controlled trial (RCT) (EF11) which was published in 2012 by Stupp et al. The Stupp study, which was sponsored and funded by the manufacturer of the device (Novocure), compared TTF therapy (delivered by the NovoTTF-100A System) with the best standard of care chemotherapy (active control). Twenty-eight clinical centers (across 7 countries) enrolled 237 adult participants with relapsed or progressive glioblastoma multiforme (GBM), despite conventional radiotherapy. Other prior treatments may have included surgery and/or chemotherapy. Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky Performance Status score of 80%. More than 80% of participants had failed 2 or more prior chemotherapy regimens ( $\geq$  second recurrence), and 20% had failed bevacizumab prior to study enrollment.



Two hundred thirty-seven patients were randomized in a 1:1 ratio to receive TTF therapy only (n=120) or active control (n=117). The choice of chemotherapy regimens varied, reflecting local practice at each of the participating clinical centers. Chemotherapy agents considered as active control during the trial included platinum-based chemotherapy (ie, carboplatin); nitrosureas; procarbazine; combination of procarbazine, lomustine and vincristine (PCV); temozolomide; and bevacizumab. For patients assigned to the TTF group, uninterrupted treatment was recommended, although patients were allowed to take treatment breaks of up to 1 hour, twice per day, for personal needs (eg, shower). In addition, patients assigned to the TTF group were allowed to take 2 to 3 days off treatment at the end of each of 4-week period (which is the minimal required treatment duration for TTF therapy to reverse tumor growth). A period of 28 days of treatment with TTF was considered 1 full treatment course.

The study was designed as a superiority trial. The primary study end point in this RCT was overall survival (OS).(3) Secondary end points included progression-free survival (PFS) at 6 months, time to progression, 1-year survival rate, quality of life (QOL), and radiological response. All end points were evaluated using intention-to-treat analysis. Participants were seen in clinic monthly, and magnetic resonance imaging (MRI) was performed after 2, 4, and 6 months from initiation of treatment, with subsequent MRIs done according to local practice until disease progression. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with the participants' caregivers were used to assess mortality rates.

Ninety-seven percent (116) of 120 participants in the TTF group started treatment and 93 participants (78%) completed 1 cycle (4 weeks) of therapy. Discontinuation of TTF therapy occurred in 27 participants (22%) due to noncompliance or the inability to handle the device.(3) For each TTF treatment month, the median compliance was 86% (range, 41%-98%), which equaled a mean use of 20.6 hours per day. In the active control group, 113 (97%) of the 117 assigned participants received chemotherapy and all except 1 individual completed a full treatment course. Twenty-one participants (18%) in the active control group did not return to the treating site and details on disease progression and toxicity were not available.

We summarize study outcomes in Table 1.

**Table 1. Randomized Trial of TTF Versus Physicians' Choice Chemotherapy in Recurrent Glioblastoma: Principal Efficacy Results From Stupp et al**

Outcomes	TTF	Chemotherapy	Measure of Association, Significance
Median survival, mo	6.6	6.0	
Hazard ratio survival			0.86 (95% CI, 0.66 to 1.12) favors TTF
Radiologic response (not all patients evaluated)	14%	9.6%	p=0.19
Median PFS, mo	2.2	2.1	
Hazard ratio PFS			0.81 (95% CI, 0.60 to 1.09) favors TTF

CI: confidence interval; PFS: progression-free survival; TTF: tumor treatment fields.

The trial did not reach its primary end point of improved survival compared to active chemotherapy. With a median follow-up of 39 months, 220 participants (93%) had died. Median survival was 6.6 months in the TTF group compared to 6.0 months in the active control group (hazard ratio, 0.86; 95% confidence interval [CI], 0.66 to 1.12; p=0.27). For both groups, 1-year survival was 20%. The survival rates for 2- and 3-year survival were 8% and 4%, respectively, for the TTF group versus 5% and 1%, respectively, for the active control group. PFS rate at 6 months was 21.4% in the TTF group, compared to 15.1% in the active control



group ( $p=0.13$ ). Objective radiological responses (partial and complete response) were noted in 14 participants in the TTF group and 7 in the active control group, with a calculated response rate of 14.0% (95% CI, 7.9% to 22.4%) compared to 9.6% (95% CI, 3.9% to 18.8%), respectively. Sixteen percent of the TTF participants had grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids. Active control participants experienced grade 2-4 events by organ system related to the pharmacologic activity of chemotherapy agents utilized; severe (grades 3 and 4) toxicity was observed in 3% of participants.

Longitudinal QOL data were available in 63 participants (27%). There were no meaningful differences observed between the groups in the domains of global health and social functioning. However, cognitive, emotional, and role functioning favored TTF therapy; physical functioning favored chemotherapy. Symptom scale analysis was in accordance to treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the TTF group.

Wong et al published a subgroup analysis of the Stupp RCT (previously described) to determine characteristics of responders and nonresponders in the treatment and active control groups.(9) Tumor response was assessed by the Macdonald criteria. More patients in the TTF arm were considered responders (14/120 vs 7/117 in the chemotherapy arm.) Median response time was longer for those in the TTF arm than the chemotherapy arm (7.3 months vs 5.6 months,  $p<0.001$ ), and there was a strong correlation (Pearson's  $r$ ) between response and OS in the TTF arm ( $p<0.001$ ) but not in chemotherapy arm ( $p=0.29$ ). Compared with the chemotherapy arm, a higher proportion of responders in the TTF arm had a prior low-grade histology (36% vs 0%). These differences in treatment responder groups suggest that TTF therapy may differentially benefit certain types of GBM; however, the small numbers of responders in both groups limits generalizations that can be drawn from this analysis.

A second post hoc analysis of the TTF EF-11 pivotal trial data was performed to evaluate OS rates among patients who completed at least 1 complete course of TTF or chemotherapy. (10) Investigators analyzed survival in what they referred to as a "modified ITT [intention-to-treat]" subgroup comprising 93 of 120 (78%) of the original TTF allocated group, versus 117 of 117 (100%) of the original chemotherapy allocated group. This exercise revealed median OS of 7.7 months in the TTF modified ITT (mITT) group compared with 5.9 months in the chemotherapy group (HR=0.69; 95% CI, 0.52 to 0.91;  $p=0.009$ ). They also showed a trend relationship between proportion of patients with higher TTF compliance and median OS rates ( $p=0.039$ ). The investigators suggest that TTF provides an OS benefit if used as intended in the FDA-approved label when compared with best chemotherapy. This post hoc analysis is limited as it was not prespecified in the study, includes only 78% of the original TTF allocated patients, and fails to control for noncompliance due to faster clinical deterioration of TTF recipients leading to treatment cessation.

### **Noncomparative Studies**

Two nonrandomized studies were identified that compared TTF treatment with standard care using historical controls. A study published in late 2014 included OS data from 457 patients included in the Patient Registry Dataset (PRiDe), a postmarketing registry of all recurrent GBM patients who received NovoTTF therapy in a real-world, clinical practice setting in 91 centers in the United States between October 2011 and November 2013.(11) The median OS rate in the PRiDe clinical practice dataset was reported as significantly superior to that attained in the TTF



EF-11 pivotal trial (9.6 months vs 6.6 months; HR=0.66, 95% CI, 0.05 to 0.86;  $p<0.001$ ). One- and 2-year OS rates for TTF in PRiDe were significantly longer than those in the TTF group in the EF-11 trial (44% vs 20% at 1 year; 30% vs 9% at 2 years, respectively). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

Kirson et al (2007) reported the findings of a study examining the effects of TTF therapy delivered by the NovoTTF-100A System in 10 patients with recurrent glioblastoma multiforme (GBM).(12) Median time to progression (TTP) in these patients was 26.1 weeks and median overall survival (OS) was 62.2 weeks. The authors noted that these TTP and OS values were more than double the reported medians of historical control patients. No device-related serious adverse events were seen after more than 70 months of cumulative treatment in all of the patients. The only device-related adverse event observed was a mild-to-moderate contact dermatitis beneath the field delivering electrodes. The primary limitation of this study was the use of historical controls, since the patients included may not be comparable on major clinical and prognostic features.

Two small case series have been published of long-term survival (>6 years) with TTF therapy.(14,15) Rulseh et al reported long-term (>7 year) survival in 4 of 20 patients with GBM who were treated with TTF,(14) while Villano et al describe 1 patient with recurrent GBM who was tumor-free more than 6 years after treatment with TTF.(15)

### **Section Summary: TTF Therapy as an Alternative to Chemotherapy for Progressive or Recurrent GBM**

Multiple case reports and small case series have concluded that TTF treatments are similar to outcomes following standard chemotherapy, with a decrease in toxicity and increase in quality of life favoring TTF.(16) Although global health and social functioning didn't show meaningful differences, cognitive, emotional and role functioning favored TTF therapy. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the TTF group.

Treatment-associated toxicity such as appetite loss, diarrhea, constipation, nausea and vomiting were directly related to the chemotherapy administration, but not reported with the TTF. The most common side effect reported during TTF treatment was a mild-to-moderate contact dermatitis beneath the field delivering electrodes. Overall, TTF yielded a longer OS in recurrent and advance GBM when compared to chemotherapy. TTF appears to provide an OS benefit when used as intended per the FDA approval.

### **TTF THERAPY AS AN ADJUNCT TO STANDARD MAINTENANCE CARE FOR GBM**

In 2015, Stupp et al published a planned interim analysis of a multicenter, open-label RCT that evaluated maintenance therapy with TTF for GBM. (13) This trial enrolled patients with GBM who had completed standard treatment consisting of biopsy or surgical resection followed by chemoradiotherapy with temozolomide. A Karnofsky Performance Status score of 70% or higher was an additional inclusion criterion. Patients were randomized in a 2:1 fashion to TTF plus temozolomide or to temozolomide alone. At the time of the interim analysis, 210 patients were randomized to TTF plus temozolomide and 105 patients to temozolomide alone. The primary outcome was PFS analyzed by intention-to-treat; a secondary outcome was OS analyzed by per-protocol analysis.

Patients in the TTF group received continuous TTF therapy delivered mainly in the home setting. Patients were trained on use of the device, including changing the electrodes, and then



treatment continued at home. Patients were encouraged to wear the device continuously, with the exception of short breaks to attend to personal needs. All patients were seen monthly for follow-up. Further, MRI was performed every 2 months and QOL measures administered every 3 months. Tumor progression was adjudicated by a central review committee blinded to treatment group.

Planned interim analysis was performed at a median follow-up of 38 months (range, 18-60 months). Median PFS and median OS are summarized in Table 2.

**Table 2. TTF Therapy as an Adjunct to Standard Maintenance Care in Glioblastoma Multiforme**

Group	N	Progression-Free Survival (95% CI), mo	Hazard Ratio (98.7% CI)	Overall Survival (95% CI), mo	Hazard Ratio (99.4% CI)
TTF + temozolomide	210 (196 <sup>a</sup> )	7.1 (5.9 to 8.2)	0.62 (0.43 to 0.89)	20.5 (16.7 to 25)	0.64 (0.42 to 0.98)
Temozolomide alone	105 (84 <sup>a</sup> )	4.0 mo (3.3 to 5.2)		15.6 mo (13.3 to 19.1)	

CI: confidence interval; TTF: tumor treatment fields.

<sup>a</sup> Included in per-protocol analysis.

There were 35 (11%) dropouts during the trial - 14 (6.7%) of 210 patients in the TTF group and 21 (20%) of 105 in the temozolomide-alone group. Adherence to treatment was defined as wearing the device for at least 18 hours a day, and 157 (75%) of 210 patients met this adherence criterion. The number of treatment cycles with temozolomide differed between groups. The TTF group received a median of 6 cycles compared with a median of 4 cycles for the temozolomide-alone group. The most common side effect of treatment was local skin irritation, which occurred in 43% of patients treated with TTF.

In October 2014, the trial independent data and safety monitoring committee reviewed the interim analysis, concluding that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended trial termination. The FDA approved study termination and the trial was closed to recruitment that November after 695 of the planned 700 participants had been randomized. All patients in the control maintenance therapy arm could crossover to receive TTFs. At the time of the Stupp interim analysis, 35 control arm participants had crossed over. FDA considered the results of this analysis for the 2015 expanded approval of Optune.

### **Section Summary: TTF Therapy as an Adjunct to Standard Maintenance Care for GBM**

The single RCT for this indication reports that PFS is improved by 3.1 months and OS is improved by 4.9 months after the addition of TTF to standard maintenance therapy (ie, temozolomide). Therefore, there may be a survival benefit associated with TTF for this indication.

### **SUMMARY OF EVIDENCE**

The evidence for tumor-treatment field therapy in patients who have recurrent or progressive glioblastoma multiforme includes 1 randomized controlled superiority pivotal trial using the U.S. Food and Drug Administration– approved device and a number of small observational studies. Relevant outcomes include overall survival (OS), quality of life (QOL), and treatment-related morbidity. GBM is the most common brain tumor, has a low quality of life during the course of treatment and has a poor prognosis. TTF therapy offers a noninvasive approach to newly diagnosed and recurrent tumors. In 2011 the FDA approved TTF therapy for use in recurrent



tumors. In 2015 the FDA expanded its recommendations for use in newly diagnosed GBM which meet specified criteria.

Studies indicated that patients treated with the device and TMZ had a longer progression-free survival of 3.1 months and an overall survival of 4.9 months longer than those who were treated with only TMZ. For individuals who have advanced or recurrent GBM and receive TTF as an alternative to standard chemotherapy, no difference was noted in overall survival.

Furthermore, there is consensus within the National Comprehensive Cancer Network that indicates consideration of alternating electric field therapy in the treatment of a recurrent glioblastoma brain tumor is appropriate.

The use of TTF therapy has been described in a number of case series. High quality studies are difficult to obtain related to the mortality rate associated with GBM. Published studies indicate that some patients who underwent TTF therapy achieved long-term survival of > 5-7 years. TTF therapy appeared to offer a higher survival rate than chemotherapy alone with the only side effect being contact dermatitis of the scalp; thus, offering a better outcome through increased quality and quantity of life.

## ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 3.

**Table 3. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
NCT01894061 <sup>a</sup>	A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma	40	Dec 2017
NCT01756729 <sup>a</sup>	A Prospective, Non-randomized, Concurrent Control, Open Label, Post-approval Study of NovoTTF-100A in Recurrent GBM Patient	486	Jan 2018
NCT02743078 <sup>a</sup>	Phase II Trial Of Optune® Plus Bevacizumab In Bevacizumab-Refractory Recurrent Glioblastoma	85	Apr 2018
NCT01954576	A Phase II Study of the NovoTTF-100A system, Enhanced by Genomic Analysis to Identify the Genetic Signature of Response in the Treatment of Recurrent Glioblastoma Multiforme	30	May 2018
NCT02663271 <sup>a</sup>	A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFields and Pulsed Bevacizumab Treatment in Patients With Bevacizumab-refractory Recurrent Glioblastoma	25	May 2018
NCT02893137 <sup>a</sup>	Phase 1 Enhancing Optune Therapy of Recurrent Glioblastoma Multiforme Using Targeted Surgical Skull Remodeling	15	Oct 2019
NCT01925573 <sup>a</sup>	Proposed Pilot Study of Combined Optune+ Bevacizumab, and Hypofractionated Stereotactic Irradiation for Bevacizumab-Naive Recurrent Glioblastoma	27	Dec 2021

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.



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## Supplemental Information

### CLINICAL INPUT RECEIVED FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests for input on the use of TTF for treatment of GBM in 2016, BCBSA received input from 1 academic medical center and 3 physician specialty societies, with a total of 9 individual responses. There was majority support, but not consensus, for use of TTF as an adjunct to maintenance treatment following initial therapy for GBM. There was mixed support for use of TTF as an alternative to chemotherapy in advanced or recurrent GBM.

### PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2016) (2) include a recommendation for the treatment of glioblastoma. For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate MGMT promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric currents therapy is a category 2A recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a 2B recommendation.

### U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

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## Government Regulations

### National:

There is no national coverage determination for TTF.

### Local:

Tumor Treatment Field Therapy

**L34823**; Effective: October 2015, Revised 1/1/17

Tumor treatment field therapy (E0766) will be denied as not reasonable and necessary.

**A52711** Effective date: 10/01/15, Revised 1/1/17

### NON-MEDICAL NECESSITY COVERAGE AND PAYMENT RULES:

For any item to be covered by Medicare, it must 1) be eligible for a defined Medicare benefit category, 2) be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member, and 3) meet all other applicable Medicare statutory and regulatory requirements.

Information provided in this policy article relates to determinations other than those based on



Social Security Act §1862(a)(1)(A) provisions (i.e. “reasonable and necessary”). TUMOR TREATMENT FIELD therapy devices are covered under the Durable Medical Equipment benefit (Social Security Act §1861(s)[6]). In order for a beneficiary’s equipment to be eligible for reimbursement the reasonable and necessary (R&N) requirements set out in the related Local Coverage Determination must be met. In addition, there are specific statutory payment policy requirements, discussed below, that also must be met.

Code E0766 is in the frequent and substantial service payment category. Items included in this payment category are reimbursed a single monthly fee schedule amount for the device and all related supplies and accessories. Separate billing of supplies and/or accessories will be denied as unbundling.

Code A4555 is not valid for billing to Medicare. If code A4555 is billed, it will be denied as an invalid code.

### **Michigan Department of Health & Human Services:**

Codes E0766 and A4555 are not listed on the MDHHS DME POS fee schedule.

*(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)*

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### **Related Policies**

N/A

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*The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 10/05/2017, the date the research was completed.*



### Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/14	4/8/14	4/15/14	Joint policy established
9/1/15	6/19/15	7/16/15	Routine review
5/1/16	2/16/16	2/23/16	<ul style="list-style-type: none"> <li>• Updated to reflect new FDA indications (2015);</li> <li>• Diverge from BCBSA;</li> <li>• Converted from Investigational to Mixed (per new FDA indications);</li> <li>• Codes added to inclusions and exclusions</li> </ul>
5/1/17	3/8/17	3/16/17	<ul style="list-style-type: none"> <li>• Routine maintenance</li> <li>• 95199 added – placement of Novo-Tal pads</li> <li>• Continue to diverge from BCBSA</li> <li>• References and rationale updated</li> </ul>
5/1/18	2/20/18	2/20/18	<ul style="list-style-type: none"> <li>• Routine maintenance</li> </ul>

Next Review Date: 1<sup>st</sup> Qtr, 2019



**BLUE CARE NETWORK BENEFIT COVERAGE**  
**POLICY: TUMOR-TREATMENT FIELDS THERAPY FOR GLIOBLASTOMA**

**I. Coverage Determination:**

<b>Commercial HMO (includes Self-Funded groups unless otherwise specified)</b>	Covered; criteria apply
<b>BCNA (Medicare Advantage)</b>	Refer to the Medicare information under the Government Regulations section of this policy.
<b>BCN65 (Medicare Complementary)</b>	Coinsurance covered if primary Medicare covers the service.

**II. Administrative Guidelines:**

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.



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Medical Policy:	II-164-003
Topic:	Tumor Treatment Fields Therapy
Section:	Medicine
Effective Date:	March 27, 2017
Issue Date:	March 27, 2017
Last Reviewed:	March 2017

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Tumor treatment fields (TTF) therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency. The use of TTF is proposed to inhibit rapidly dividing tumor cells by arresting cell proliferation, leading to destruction of cells.

Optune™ (formerly known as the NovoTTF-100A™ System) received premarket approval (PMA) from the U.S. Food and Drug Administration (FDA) in 2011 as a treatment for adult patients (22 years of age or older) with confirmed glioblastoma multiforme (GBM), following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment, and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted. In October 2015, the FDA approved the Optune™ with temozolomide for the treatment of adult patients (22 years of age or older) with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

Glioblastoma is also known as glioblastoma multiforme (GBM). The term "multiforme" is no longer part of the World Health Organization (WHO) designation, though glioblastoma is still often abbreviated "GBM." Glioblastoma is the most common form of malignant primary brain tumor in adults, and comprises approximately 15% of all brain and central nervous system tumors. Glioblastoma is a WHO grade IV astrocytoma, the most deadly type of glial cell tumor, which is often resistant to standard chemotherapy.

Tumor treatment fields therapy for glioblastoma is delivered by a battery-powered, portable device that generates the electrical fields via disposable electrodes that are noninvasively attached to the patient's shaved scalp over the site of the tumor. The device is used by the patient at home on a continuous basis (20-24 hours per day) for the duration of treatment, which can last for several months. The use of TTF is also under investigation for several other types of malignancies, including cancers of the breast, lung, ovaries and pancreas, as well as melanoma and solid tumor brain metastases.

*This policy is designed to address medical guidelines that are appropriate for the majority of individuals with a particular disease, illness, or condition. Each person's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.*

**Policy Position:** Coverage is subject to the specific terms of the member's benefit plan.



**I. Tumor treatment fields (TTF) therapy may be considered **MEDICALLY NECESSARY** for patients who meet **ALL** of the following criteria:**

- History of histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma); **AND**
- Recurrence of glioblastoma in the supratentorial region of the brain has been histologically or radiologically confirmed; **AND**
- After surgery, radiation and chemotherapy, or patient is not a candidate for these treatments.

**II. Tumor treatment fields (TTF) therapy is considered **INVESTIGATIVE** for all other indications including, but not limited to treatment of other malignancies (e.g., cancers of the breast, lung, ovaries, pancreas, melanoma and solid tumor brain metastases). There is a lack of evidence demonstrating an impact on improved health outcomes for treatment of conditions other than recurrent glioblastoma.**

### **Procedure Codes**

A4555, E0766

### **Denial Statements**

No additional statements.

### **Links**

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*Blue Cross and Blue Shield of Minnesota medical policies apply generally to all Blue Cross and Blue Plus plans and products. Benefit plans vary in coverage and some plans may not provide coverage for certain services addressed in the medical policies.*

*Medicaid products and some self-insured plans may have additional policies and prior authorization requirements. As applicable, review the provisions relating to a specific coverage determination, including exclusions and limitations. Note that services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial of claims may result if criteria are not met.*

*For Medicare NCD and/or Medicare LCD, please consult CMS or National Government Services websites.*

*Blue Cross and Blue Shield of Minnesota reserves the right to revise, update and /or add to its medical policies at any time without notice. Codes listed on this policy are included for informational purposes only, and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. These guidelines are the proprietary information of Blue Cross and Blue Shield of Minnesota. Any sale, copying or dissemination of the medical policies is prohibited; however, limited copying of medical policies is permitted for individual use.*



## Corporate Medical Policy

### Tumor-Treatment Fields Therapy

**File Name:** tumor\_treatment\_fields\_therapy  
**Origination:** 9/2013  
**Last CAP Review:** 11/2017  
**Next CAP Review:** 11/2018  
**Last Review:** 6/2018

#### Description of Procedure or Service

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Tumor-treatment fields therapy is a noninvasive technology that uses alternating electrical fields. It is used to treat glioblastoma multiforme, and has been proposed for use in other tumor types.

##### **Background**

Glioblastoma, also known as glioblastoma multiforme (GBM), is the most common form of malignant primary brain tumor in adults, comprising approximately 15% of all brain and central nervous system tumors and more than 50% of all tumors that arise from glial cells. The peak incidence for GBM occurs between the ages of 45 and 70 years. GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor, which is often resistant to standard chemotherapy. According to the National Comprehensive Cancer Network (NCCN), GBM is the "deadliest brain tumor with only a third of patients surviving for one year and less than 5% living beyond 5 years."

The primary treatment for newly diagnosed GBM is debulking surgery to remove as much of the tumor as possible. At the time of surgery, some patients may undergo implantation of the tumor cavity with a carmustine (BCNU) -impregnated wafer. Depending on the patient's physical condition, adjuvant radiation therapy, chemotherapy (typically temozolomide), or a combination of the two is recommended. After adjuvant therapy, some patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles.

No standard treatment exists for recurrent GBM. In patients with disease that recurs after these initial therapies, additional debulking surgery may be used if recurrence is localized. Other treatment options for recurrent disease include various forms of systemic medications such as bevacizumab, bevacizumab plus chemotherapy (e.g., irinotecan, BCNU/CCNU, temozolomide), temozolomide, nitrosourea, PCV (procarbazine, CCNU, and vincristine), cyclophosphamide, and platinum-based agents. External beam radiotherapy also may be used to treat recurrent GBM. Response rates in recurrent disease are less than 10%, and progression-free survival rates at 6 months are less than 20%.

Tumor-treatment fields (TTF) therapy is a noninvasive technology that is intended to treat GBM on an outpatient basis using electrical fields. TTF therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis. Tumor-treatment fields are proposed to inhibit rapidly dividing tumor cells by two mechanisms, arrest of cell proliferation and destruction of cells while undergoing division.

The NovoTTF-100A™ System (Novocure Ltd., Haifa, Israel) has been approved by the U.S. Food and Drug Administration (FDA) to deliver TTF therapy. TTF therapy via the NovoTTF-



# Tumor-Treatment Fields Therapy

100A™ System is delivered by a battery-powered, portable device that generates the fields via disposable electrodes that are noninvasively attached to the patient's shaved scalp over the site of the tumor. The device is used by the patient at home on a continuous basis (20–24 hours per day) for the duration of treatment, which can last for several months. Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living.

## **Regulatory Status**

The NovoTTF-100A™ System (assigned the generic name of tumor-treatment fields) was approved by the FDA in April 2011 through the premarket approval process. The FDA-approved indication for use is: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment, and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved a request for Novocure to change its products name from Novo-TTF-110A System to Optune™.

In October 2015, FDA expanded the indication for Novocure's use of Optune in combination with temozolomide for newly diagnosed glioblastoma.

## **Related Policies**

Analysis of MGMT Promoter Methylation in Malignant Gliomas

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

## **Policy**

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**BCBSNC will provide coverage for tumor treatment fields therapy when it is determined to be medically necessary because the medical criteria shown below are met.**

## **Benefits Application**

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## **When Tumor-Treatment Fields Therapy is covered**

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Tumor treatment fields (TTF) therapy is considered to be **medically necessary** for the treatment of newly diagnosed, supratentorial glioblastoma multiforme, as an adjunct to standard maintenance therapy with temozolomide when **ALL** of the following conditions are met:

- The patient has completed initial treatment with surgery, radiation therapy and concomitant chemotherapy; **AND**
- The patient is  $\geq 18$  years of age; **AND**
- Has a Karnofsky Performance Status score  $\geq 70\%$ ; **AND**
- There is documentation of lack of tumor progression following radiation and chemotherapy (see Policy Guidelines); **AND**
- The individual is willing and capable of wearing the device for at least 18 hours a day.



# Tumor-Treatment Fields Therapy

## When Tumor-Treatment Fields Therapy is not covered

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Tumor treatment fields therapy (TTF) is considered investigational, including, but not limited to, the following situations:

- As an alternative or an adjunct to standard medical therapy (eg bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme.
- In the treatment of other types of malignant tumors, including but not limited to, pancreatic adenocarcinoma, lung cancer and brain metastases.

## Policy Guidelines

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In the EF-14 trial, tumor progression following radiochemotherapy was defined as 25% or more increase in enhancing lesions or any new lesions, as determined by imaging.

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment with surgery, radiotherapy, and/or chemotherapy who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes an RCT. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

## Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: A4555, E0766*



# Tumor-Treatment Fields Therapy

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

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BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 8/8/2013

Specialty Matched Consultant – 9/2013

Senior Medical Director – 9/2013

Specialty Matched Consultant Advisory Panel – 11/2013

BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 8/14/14

Specialty Matched Consultant Advisory Panel – 11/2014

BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 8/13/15

Specialty Matched Consultant Advisory Panel- 11/2015

BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 8/11/16

Specialty Matched Consultant Advisory Panel- 11/2016

BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 7/13/17

Specialty Matched Consultant Advisory Panel- 11/2017

BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 6/14/18

Medical Director review 6/18/18

## Policy Implementation/Update Information

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### **For Policy Titled: Tumor-Treatment Fields Therapy for Glioblastoma**

10/1/13 New policy. Tumor treatment fields therapy to treat glioblastoma is considered investigational. Senior Medical Director review 8/30/2013. Specialty Matched Consultant review 9/18/2013. (btw)

12/10/13 Specialty Matched Consultant Advisory Panel review 11/20/2013. No change to policy statement. (btw)

12/31/13 Added new HCPCS codes, A4555 and E0766, to the Billing/Coding section. Removed the following statement from the Billing/Coding section; “Providers will most likely use E1399 and A9900 for claim submission.” (btw)

12/9/14 Specialty Matched Consultant Advisory Panel review 11/24/2014. No change to policy intent. Reference added. (lpr)



# Tumor-Treatment Fields Therapy

- 12/30/15 Updated Policy Guidelines. Specialty Matched Consultant Advisory Panel review 11/18/2015. Reference added. No change to policy statement. (lpr)
- 12/30/16 Updated Policy Guidelines, Description and Regulatory status. Clarified non-covered indications. Reference added. Medical Director review 9/2016. Specialty Matched Consultant Advisory Panel review 11/30/2016. No change to policy intent. (lpr)
- 8/11/17 Updated Policy Guidelines section. Clarified policy statement: 1) as an alternative to standard chemotherapy for patients with progressive or recurrent glioblastoma multiforme after initial or repeat treatment with surgery, radiotherapy, and/or chemotherapy; 2) as an adjunct to standard maintenance therapy in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy and/or chemotherapy. No change to policy intent and the service remains investigational. Reference added. (lpr)
- 8/25/17 Under “When Not Covered” section: clarified investigational indications. No change to policy intent. (lpr)
- 12/15/17 Specialty Matched Consultant Advisory Panel review 11/29/2017. No change to policy statement. (lpr)

## **For Policy Titled: Tumor-Treatment Fields Therapy**

- 06/29/18 Updated Description and Policy Guidelines sections. Under “When Covered section, revised policy statement to reflect medical necessity coverage for the treatment of newly diagnosed, supratentorial glioblastoma multiforme, as an adjunct to standard maintenance therapy with temozolomide when **ALL** of the following conditions are met: The patient has completed initial treatment with surgery, radiation therapy, and concomitant chemotherapy; **AND**; The patient is  $\geq 18$  years of age; **AND**; Has a Karnofsky Performance Status score  $\geq 70\%$ ; **AND**; There is documentation of lack of tumor progression following radiation and chemotherapy (see Policy Guidelines); **AND**; the individual is willing and capable of wearing the device for at least 18 hours a day. **Title changed from “Tumor-Treatment Fields Therapy for Glioblastoma” to “Tumor-Treatment Fields Therapy.** Reference added. Medical Director review 6/18/18. (lpr)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.



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Medical Policy

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## Tumor Treatment Fields (TTF)

**Section:** Durable Medical Equipment

**Effective Date:** November 1, 2018

**Issued Date:** September 26, 2018

Electrical fields, known as “tumor treatment fields” (TTF), are created by low-intensity, alternating intermediate frequency (100-200 kilohertz [kHz]) electric currents delivered to the malignant tumor site by insulated electrodes placed on skin surface of the tumor site. As a result of the unique shape and electrical characteristics of dividing tumor cells, TTF exposure may damage the dividing cells through anti-microtubule mechanisms and could stop tumor growth while sparing normal tissue.

### Policy Position

TTF may be considered medically necessary when **ALL** of the following indications are met:

- When it is used as an alternative to standard medical therapy, as a monotherapy; **and**
- For treatment of adult patients (22 years of age or older); **and**
- With histologically-confirmed glioblastoma multiforme; **and**
- Following histologically- or radiologically-confirmed recurrence in the Supratentorial region of the brain; **and**
- After receiving chemotherapy; **and**
- After surgical and radiation options have been exhausted.

**OR**

TTF may be considered medically necessary when **ALL** of the following indications are met:

- It is used as an adjunct to standard maintenance therapy; **and**
- For treatment for adult patients (22 years of age or older); **and**
- With histologically-confirmed glioblastoma multiforme; **and**
- When it is used with temozolomide; **and**
- With newly diagnosed, supratentorial glioblastoma, **and**
- Following maximal debulking surgery; **and**
- Completion of radiation therapy; **and**
- Together with concomitant standard of care chemotherapy.

TTF is considered experimental/investigational when above criteria are not met or for any other indications, and therefore, not covered because the safety and/or effectiveness of this service cannot be established by the available published peer-reviewed literature.

### Procedure Codes



## A4555, E0766

**Covered Diagnosis Codes for Procedure Codes A4555 and E0766**

C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles
C71.1	Malignant neoplasm of frontal lobe
C71.2	Malignant neoplasm of temporal lobe
C71.3	Malignant neoplasm of parietal lobe
C71.4	Malignant neoplasm of occipital lobe
C71.5	Malignant neoplasm of cerebral ventricle
C71.6	Malignant neoplasm of cerebellum
C71.7	Malignant neoplasm of brain stem
C71.8	Malignant neoplasm of overlapping sites of brain
C71.9	Malignant neoplasm of brain, unspecified

**Place of Service: Inpatient/Outpatient**

Experimental/Investigational (E/I) services are not covered regardless of place of service.

The use of tumor treatment fields is typically an outpatient procedure which is only eligible for coverage as an inpatient procedure in special circumstances, including, but not limited to, the presence of a co-morbid condition that would require monitoring in a more controlled environment such as the inpatient setting.

**Denial Statements**

Services that do not meet the criteria of this policy will be considered experimental/investigational (E/I). A network provider can bill the member for the experimental/investigational service. The provider must give advance written notice informing the member that the service has been deemed E/I. The member must be provided with an estimate of the cost and the member must agree in writing to assume financial responsibility in advance of receiving the service. The signed agreement must be maintained in the provider's records.

**Links**

- [Reference \(pdf\)](#)

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**EFFECTIVE DATE:** 10|01|2018  
**POLICY LAST UPDATED:** 08|07|2018

## OVERVIEW

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (ITF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

## MEDICAL CRITERIA

### BlueCHiP for Medicare and Commercial Products:

Tumor treating fields therapy to treat glioblastoma multiforme is considered medically necessary as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy when **all** of the following criteria are met:

- Adult patients  $\geq 18$  years of age
- Supratentorial tumor
- Karnofsky Performance Status score  $\geq 70\%$  \*
- Patient understands device use, including the requirement for a shaved head, and is willing to comply with to the Food and Drug Administration label guideline to use Optune for at least 18 hours a day and should finish at least 4 full weeks of therapy to get the best response to treatment.

**APPROVAL PERIOD:** 6 months. Services beyond the 6 months will need a new review and meet the above criteria.

### \*KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

- 100 Normal no complaints; no evidence of disease.
- 90 Able to carry on normal activity; minor signs or symptoms of disease. Able to carry on normal activity and to work; no special care needed.
- 80 Normal activity with effort; some signs or symptoms of disease.
- 70 Cares for self; unable to carry on normal activity or to do active work.
- 60 Requires occasional assistance, but is able to care for most of his personal needs. Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.
- 50 Requires considerable assistance and frequent medical care.
- 40 Disabled; requires special care and assistance.
- 30 Severely disabled; hospital admission is indicated although death not imminent.
- 20 Very sick; hospital admission necessary; active supportive treatment necessary.
- 10 Moribund; fatal processes progressing rapidly. Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.
- 0 Dead

## PRIOR AUTHORIZATION



Prior authorization is required for BlueCHiP for Medicare and recommended for Commercial Products

## **POLICY STATEMENT**

### **BlueCHiP for Medicare and Commercial Products:**

Tumor treating fields therapy is medically necessary when the above criteria is met.

### **BlueCHiP for Medicare**

Tumor treating fields therapy is considered not covered in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (eg, bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
- For brain metastases
- For cancer in areas other than the brain.

### **Commercial Products:**

Tumor treating fields therapy is considered not medically necessary in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (eg, bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
- For brain metastases
- For cancer in areas other than the brain.

## **COVERAGE**

Benefits vary between groups/contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for services not medically necessary or not covered

## **BACKGROUND**

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes a randomized controlled trial (RCT). Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in



chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

## **CODING**

### **BlueCHiP for Medicare and Commercial Products**

The following code is medically necessary/covered when criteria is met.

**E0766:** Electrical stimulation device used for cancer treatment, includes all accessories, any type

The following code is covered when the service is approved

**A4555:** Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only

## **RELATED POLICIES**

None

## **PUBLISHED**

Provider Update, September 2018

Provider Update, September 2017

Provider Update, October 2016

Provider Update, April 2015

Provider Update, March 2014

## **REFERENCES**

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**MEDICAL COVERAGE POLICY | 4**



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CAM 042      Electric Tumor Treatment Field (TTF)

Category:      Radiology      Last Reviewed: July 2013

Department(s): Medical Affairs      Next Review:      July 2014

Original Date: July 2013

## Description:

Electrical fields known as "tumor treatment fields (TTF)" are created by low-intensity, alternating intermediate frequency (100 – 200 kilohertz [kHz]) electric currents delivered to the malignant tumor site by insulated electrodes placed on skin surface of the tumor site. As a result of the unique shape and electrical characteristics of dividing tumor cells, TTF exposure may damage the dividing cells through anti-microtubule mechanisms and could stop tumor growth while sparing normal tissue.

## Policy:

The use of devices to generate electric tumor treatment fields (ETTF) is **MEDICALLY NECESSARY** as monotherapy for persons with histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma), after histologically or radiologically confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy.

The use of devices to generate electric tumor treating fields (TTF) as a treatment for malignant tumors is considered **INVESTIGATIONAL** for all other indications.

## Rationale:

The use of electric fields and the corresponding effects upon living tissue has been studied in the laboratory and clinical settings. Alternating electric fields at very low frequencies (below one kHz) stimulate excitable tissue resulting from membrane depolarization (Kirson 2004, 2007, 2009; Salzberg, 2008). Electric fields in the tens of kHz to megahertz (intermediate-frequency) alternate too fast to stimulate tissue and results in minute heating. Kirson and colleagues (2004) demonstrated targeted inhibitory effects on dividing cells with the application of alternating electric fields of very low-intensity (less than two V/centimeter [cm]) and intermediate-frequency, called TTF.

Utilizing time-lapse microphotography of mouse melanoma cell cultures, unique cellular processes as a result of TTF



exposure were identified. Prolongation of mitosis in TTF-treated cells was statistically significant, and one quarter of the treated cells was destroyed. Cellular destruction was observed only in mitotic cells, and cells at rest (quiescent) remained intact, both functionally and morphologically. Nuclear rotation was also observed in TTF treated cell cultures. Microtubules, in the form of spatially organized mitotic spindles in dividing cells, have very large electric dipole moments that may be disoriented by TTF forces. In the control cell cultures, 95 percent of the mitotic spindles were intact and exhibited normal features in cells undergoing mitosis compared to 50 percent of abnormal cell activity in TTF-treated cultures. The use of TTF was then applied in vivo, to two animal tumor models (adenocarcinoma and malignant melanoma cells). TTF-treated tumors were significantly smaller compared to the control tumor size, and the surrounding normal tissue was spared from injury. The encouraging preclinical data led to studies of electric TTF treatment in humans.

The U.S. Food and Drug Administration (FDA, 2011) approved NovoTTF-100A System (NovoCure Ltd., Haifa, Israel) as a treatment for adults with histologically-confirmed, recurrent glioblastoma multiforme (GBM) in the supratentorial region of the brain, based on data presented to the committee from a phase III, multinational, randomized, controlled pivotal clinical trial. Twenty-eight clinical centers enrolled 237 adult participants with relapsed or progressive GBM despite conventional therapy (e.g., surgery and chemo-radiotherapy followed by chemotherapy). One hundred twenty participants were randomized in a 1:1 ratio to receive NovoTTF treatment and 117 participants were randomized to the BSC group with effective chemotherapies as practiced at each of the participating clinical centers. Chemotherapy agents considered as BSC during the trial included platinum-based chemotherapy (i.e., carboplatin); nitrosureas (BCNU); procarbazine; combination of procarbazine, lomustine and vincristine (PCV); temozolomide; and bevacizumab. A period of twenty-eight-days of treatment with NovoTTF was considered one full treatment course. Participants treated with NovoTTF were allowed to take breaks from treatment up to an hour, twice per day for personal needs such as showers. The primary endpoint of the study was overall survival (OS). Secondary endpoints included progression free survival rates at 6-months (PFS6); time to progression (TTP), 1-year survival rate; quality of life (QOL); and radiological response. Participants were seen in clinic monthly, and magnetic resonance imaging (MRI) was performed after 2, four and six months from initiation of treatment and subsequent MRIs were done according to local practice until disease progression. Medical follow-up continued for two months after disease progression. Monthly telephone interviews with the participants' caregivers were used to assess participant mortality rates.

Of the 237 enrollees, eight participants (4 in each group) did not receive the assigned therapy. Ninety-7 percent (116) of 120 enrollees in the NovoTTF group started treatment and 93 participants (78 percent) completed one cycle (4 weeks) of therapy. Discontinuation of TTF occurred in 27 participants due to noncompliance or the inability to handle the device. For each TTF treatment month, the median compliance was 86 percent (range 41-98 percent), which equaled a mean use of 20.6 hours per day. In the BSC (active control) group, 113 (97 percent) of the 117 assigned participants received chemotherapy and all completed one full treatment course with the exception of one individual. In the BSC cohort, 21 participants did not return to the site and details on disease progression and toxicity were not available. Stupp and colleagues (2012) noted the median survival of 6.6 months in the TTF group was marginally higher than six months in the BSC group (hazard ratio 0.86 [95 percent confidence interval [CI] 0.66 – 1.12];  $p=0.27$ ). For both groups, one-year survival was 20 percent. The survival rates for 2- and 3-years were 8 percent (95 percent CI 4, 13) and 4 percent (95 percent CI 1, 8) versus 5 percent (95 percent CI 3, 10) and 1 percent (95 percent CI 0, 3) for the TTF cohort compared to the BSC cohort, respectively. With a median follow-up of 39 months, 93 percent (220 participants) had died. Objective radiological responses (partial and complete response) were noted in 14 participants in the TTF group and seven in the BSC group, with a calculated response rate of 14.0 percent (95 percent CI 7.9- 22.4 percent) compared to 9.6 percent (95 percent CI 3.9 – 18.8 percent), respectively. Sixteen percent of the TTF participants had grade one and two contact



dermatitis on the scalp, which resolved with topical steroids. BSC participants experienced grade 2-4 events by organ system related to the pharmacologic activity of chemotherapy agents utilized. Quality of life data were available in 63 participants (27 percent). Based on the QLQ C-30 and BN-20 questionnaires (5 out of six general scales and of nine symptom seven scales including nausea, vomiting, diarrhea, constipation and pain, quality of life was consistently higher in NovoTTF than in the control group. There were no meaningful differences observed between the domains of global health and social functioning. The BSC cohort had a larger decrease in the negative effects of seizures than the TTF cohort. The self-reporting of QOL indicators may be influenced by bias for the treatment group (FDA Label, 2011; Stupp, 2012).

In an industry-sponsored study, Kirson and colleagues (2007) reported results of TTF treatment on various tumor cell lines and animal tumor models and noted "optimal frequencies differed between cancer cell types." Additionally, the effects of a total of 280 weeks of TTF treatment on 10 individuals with recurrent GBM were reported in the pilot study. TTF treatment resulted in a median TTP of 26.1 weeks (range three – 124 weeks) and the PFS6 months of 50 percent (23 - 77 percent confidence interval). The median OS is 62.2 weeks (range 20.3 - 124.0 weeks). One individual achieved a CR and is free from tumor ten months after stopping treatment, and one participant achieved and continues to maintain a PR seven months after stopping treatment. The authors concluded TTF treatment is encouraging when compared to historical average PFS6 of  $15.3 \pm 3.8$  percent and average historical TTP of  $9.5 \pm 1.6$  weeks and an average OS  $29.3 \pm$  six weeks. Mild to moderate contact dermatitis was reported in nine out of ten participants.

In 2009, results from a pilot study of TTF alone and TTF in combination with chemotherapy for individuals with diagnosed GBM were reported (Kirson). In this single arm study, the first group included 10 individuals with recurrent GBM after failure of maintenance temozolomide (Kirson, 2007), and 10 individuals with newly diagnosed GBM treated with TTF combined with temozolomide were in the second cohort. All 20 individuals were treated for an average of one year (range 2.5 – 24 months) continuously. The first group was compared to a matched group of 18 concurrent controls who received salvage chemotherapy for relapsed/recurrent GBM. The TTF-chemotherapy group was compared to a matched group of 32 concurrent controls who received temozolomide alone. In addition, OS for both cohorts was compared to matched historical control data. Data for the first group were reported in 2007 (Kirson). For the group of 10 individuals with newly diagnosed GBM, PFS was significantly different ( $P = 0.0002$ , HR 3.32 [95 percent CI 1.9 – 5.9]) between the TTF-chemotherapy group compared to the matched concurrent and historical controls. The difference in OS was also significant ( $P=0.0018$ ). The authors concluded TTF may also be an effective sensitizer when used concurrently with chemotherapeutic agents.

A pilot study (Salzberg, 2008) included six participants with locally advanced or metastatic malignant tumors (3 cases - skin metastasis from primary breast cancer; one case each: GBM, malignant melanoma, mesothelioma). Participants had no concomitant anti-tumor therapy and had no additional standard therapy available. All six participants had a total of 128 full days of TTF treatment with individual exposure of 13 – 46 days. Compliance was greater than 80 percent. Three out of six participants had grade one skin irritation which was reversible with electrode repositioning and application of topical steroid ointments. A partial response in skin metastasis from primary breast cancer was observed in one participant. Tumor growth was arrested in three participants and one participant had progressive disease. The participant with mesothelioma had stabilization of a portion of the tumor while another part of the tumor had progressive disease. The individual with GBM did not respond to four weeks of treatment. The mixed results and minimal toxicities from TTF warranted "further investigation in larger clinical trials."

Although the NovoTTF-100A device has received FDA approval, the pivotal trial did not achieve the primary endpoint of the study, which was improved survival with NovoTTF treatment in comparison to chemotherapy. In



addition, the long-term safety and efficacy as a treatment for recurrent GBM has not been demonstrated. The expedited premarket approval (PMA) includes a requirement for a post-market non-randomized, unblinded, concurrent control study of NovoTTF-100A in individuals with recurrent GBM. The primary question to be addressed by the study (FDA Label, 2011): "Is the overall survival of patients treated with NovoTTF-100A non-inferior to the survival of patients treated with the best standard of care (chemotherapy)?" There are currently ongoing clinical trials investigating the safety and effectiveness of the novel TTF device. In addition, there are ongoing investigations to determine the optimal TTF dosing for specific tumor types; the use of TTF alone and in combination with chemotherapy agents; and its place in therapy. Currently, published articles include animal studies, in vitro studies and small case series.

Treatment recommendations published by the National Comprehensive Cancer Network<sup>®</sup> (NCCN, 2012) and the National Cancer Institute (NCI, 2012) include surgical resection, radiation therapy and/or chemotherapy as treatment options, and do not include TTF treatment for recurrent GBM.

The NovoTTF-100A System was approved by the U.S. Food and Drug Administration in April, 2011. This novel device was approved to treat adults with glioblastoma multiforme (GBM) that recurs or progresses after receiving chemotherapy and radiation therapy. TTF technology is also being studied as a treatment for other solid tumors such as non-small cell lung cancer and melanoma. There are published data from TTF use to treat tumors in pre-clinical trials and from small case series. However, there is a paucity of published evidence from randomized controlled trials comparing the long term safety and efficacy of TTF as a treatment of tumors.

According to the National Cancer Institute, glioblastoma (World Health Organization grade IV) is also known as glioblastoma multiforme (GBM). The peak incidence for GBM occurs between the ages of 45 and 70 years. Glioblastoma is highly invasive and is the most frequently occurring brain tumor accounting for approximately 12 percent to 15 percent of all brain tumors and 50 percent to 60 percent of all astrocytic tumors. Giant cell glioblastoma and gliosarcoma are two histologic variants of glioblastoma multiforme. According to the NCCN (2012) GBM is the "deadliest brain tumor with only a third of patients surviving for one year and less than 5 percent living beyond five years."

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## Tumor Treatment Fields for CNS Cancers Corporate Medical Policy

File Name: Tumor Treatment Fields for CNS Cancers  
File Code: UM.SPSVC.22  
Origination: New policy  
Last Review: 06/2018  
Next Review: 06/2019  
Effective Date: 10/01/2018

### Description/Summary

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

### Policy

#### Coding Information

Click the links below for attachments, coding tables & instructions.

[Attachment 1](#)

#### When a service may be considered medically necessary

Tumor treating fields therapy to treat glioblastoma multiforme, anaplastic oligodendroglioma, anaplastic astrocytoma, and anaplastic gliomas may be considered medically necessary, in the following situations:

- As an alternative to standard chemotherapy for patients with progressive or recurrent glioblastoma multiforme, anaplastic oligodendroglioma, anaplastic astrocytoma, and anaplastic gliomas after initial or repeat treatment with surgery, radiotherapy, and/or chemotherapy when disease is unresectable or resection not recommended.
- As adjuvant treatment to standard therapy in patients with supratentorial disease and glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy.

#### When a service is considered investigational

Tumor treating fields therapy is considered investigational for ALL other indications.



## Policy Guidelines

There are no specific codes for the initial application of this system or instruction on use. The patient reapplies the transducer arrays at home after the initial instruction.

## Reference Resources

1. Blue Cross Blue Shield Association Medical Policy Reference Manual. Tumor Treatment Fields Therapy for Glioblastoma. 1.01.29. 7:2017.
2. National Cancer Institute (NCI). Adult Central Nervous System Tumors Treatment (PDQ®)-Health Professional Version 1 2018.  
[https://www.nccn.org/professionals/physician\\_gls/pdf/cns.pdf](https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf). Accessed 5/17/18.
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## Document Precedence

Blue Cross and Blue Shield of Vermont (BCBSVT) Medical Policies are developed to provide clinical guidance and are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. The applicable **group/individual contract and member certificate language, or employer's benefit plan** if an ASO group, determines benefits that are in effect at the time of service. Since medical practices and knowledge are constantly evolving, BCBSVT reserves the right to review and revise its medical policies periodically. To the extent that there may be any conflict between **medical policy and contract/employer benefit plan language, the member's contract/employer benefit plan language** takes precedence.

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## Administrative and Contractual Guidance

### Benefit Determination Guidance

Prior approval is required and benefits are subject to all terms, limitations and conditions of the subscriber contract.

Incomplete authorization requests may result in a delay of decision pending submission of missing information. To be considered complete, see policy guidelines above.

An approved referral authorization for members of the New England Health Plan (NEHP) is required. A prior approval for Access Blue New England (ABNE) members is required. NEHP/ABNE members may have different benefits for services listed in this policy. To confirm **benefits, please contact the customer service department at the member's health plan.**

Federal Employee Program (FEP): Members may have different benefits that apply. For further information please contact FEP customer service or refer to the FEP Service Benefit **Plan Brochure. It is important to verify the member's benefits** prior to providing the service to determine if benefits are available or if there is a specific exclusion **in the member's** benefit.

**Coverage varies according to the member's group or individual contract. Not all groups are** required to follow the Vermont legislative mandates. Member Contract language takes precedence over medical policy when there is a conflict.

If the member receives benefits through an Administrative Services Only (ASO) group, benefits **may vary or not apply. To verify benefit information, please refer to the member's** employer benefit plan documents or contact the customer service department. Language in the employer benefit plan documents takes precedence over medical policy when there is a conflict.

### Policy Implementation/Update information

06/2018	New Policy, input received from external network specialty providers.
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### Eligible providers

Qualified healthcare professionals practicing within the scope of their license(s).



Approved by BCBSVT Medical Director(s )

Date Approved

Joshua Plavin, MD, MPH, MBA  
Chief Medical Officer

Attachment I

Code Type	Number	Brief Description	Policy Instructions
The following codes are considered as medically necessary when applicable criteria have been met.			
HCPCS	A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only	Prior Approval Required if over the following dollar threshold per contract.
HCPCS	E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type	Requires Prior Approval



# Protocol

## Tumor Treating Fields Therapy

(10129)

(Formerly Tumor Treatment Fields Therapy for Glioblastoma)

Medical Benefit		Effective Date: 10/01/18	Next Review Date: 07/19
Preauthorization	Yes	Review Dates: 09/15, 05/16, 09/16, 09/17, 07/18	

### Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"><li>• With newly diagnosed glioblastoma multiforme on maintenance therapy after initial treatment</li></ul>	Interventions of interest are: <ul style="list-style-type: none"><li>• Tumor treating fields therapy as an adjunct to standard maintenance therapy</li></ul>	Comparators of interest are: <ul style="list-style-type: none"><li>• Standard maintenance therapy alone</li></ul>	Relevant outcomes include: <ul style="list-style-type: none"><li>• Overall survival</li><li>• Disease-specific survival</li><li>• Quality of life</li><li>• Treatment-related morbidity</li></ul>
Individuals: <ul style="list-style-type: none"><li>• With progressive or recurrent glioblastoma multiforme</li></ul>	Interventions of interest are: <ul style="list-style-type: none"><li>• Tumor treating fields therapy as an adjunct or alternative to medical therapy</li></ul>	Comparators of interest are: <ul style="list-style-type: none"><li>• Standard medical therapy</li></ul>	Relevant outcomes include: <ul style="list-style-type: none"><li>• Overall survival</li><li>• Disease-specific survival</li><li>• Quality of life</li><li>• Treatment-related morbidity</li></ul>

### DESCRIPTION

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

### SUMMARY OF EVIDENCE

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes a randomized controlled trial (RCT). Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (i.e., temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited.



The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

## POLICY

Tumor treating fields therapy to treat glioblastoma multiforme is considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

- Adult patients  $\geq 22$  years of age
- Supratentorial tumor
- Karnofsky Performance Status score  $\geq 70\%$
- Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (see Policy Guidelines).

Tumor treating fields therapy is considered **investigational** in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (e.g., bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
- For brain metastases
- For cancer in areas other than the brain.

## POLICY GUIDELINES

Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth  $> 25\%$  compared with the smallest tumor area measured in the patient during the trial or appearance of one or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).



The Food and Drug Administration label includes the following notices:

- Patients should use Optune for at least 18 hours a day to get the best response to treatment
- Patients should finish at least four full weeks of therapy to get the best response to treatment. Stopping treatment before four weeks lowers the chances of a response to treatment.

## MEDICARE ADVANTAGE

For Medicare Advantage tumor-treatment fields therapy is considered **not medically necessary**.

## BACKGROUND

### GLIOBLASTOMA MULTIFORME

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.<sup>1</sup> GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (e.g., bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors.<sup>1</sup> The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to one year, and the five-year survival rate was around 5%.<sup>2</sup>

### Clinical Context and Therapy Purpose

The purpose of alternating electrical field therapy, more commonly known as TTF therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

### Treatment of Newly Diagnosed GBM

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these two therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for five days of every 28-day cycle for six cycles. Response and overall survival rates with temozolomide are higher in patients who have O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation.

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice.<sup>3</sup> For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially all patients.



## Treatment of Recurrent GBM

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (e.g., lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at six months is less than 20%.<sup>4</sup> There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

The questions addressed in this protocol are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

### Patients

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

### Interventions

TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields.<sup>4-6</sup> TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. TTF therapy is proposed to inhibit tumor growth by two mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase.<sup>5,6</sup> Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune (formerly NovoTTF-100A System) is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma,<sup>4</sup> disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and two to three days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is one month, with the continuation of treatment available until recurrence.

### Comparators

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.



The following practices are currently being used to make decisions about recurrent GBM: medical therapy.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds three to five months.<sup>4</sup>

#### Outcomes

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

#### Timing

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

#### Setting

The setting is outpatient care by an oncologist or neuro-oncologist.

### REGULATORY STATUS

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.<sup>7</sup> The FDA-approved label reads as follows: “The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted.”

In September 2014, the FDA approved Novocure’s request for a product name change from NovoTTF-110A System to Optune®.<sup>8</sup>

In October 2015, the FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.<sup>9</sup> The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: “This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.”

FDA product code: NZK.

### RELATED PROTOCOLS

Intensity-Modulated Radiotherapy: Central Nervous System Tumors

Intracavitary Balloon Catheter Brain Brachytherapy for Malignant Gliomas



## Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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## Corporate Medical Policy

### Title: Tumor Treating Fields Therapy Policy # 1.01.29.0

**Last Review:** July 2018

**Next Review:** July 2019

#### POLICY DISCLAIMER

Current medical policy is to be used in determining a Member's contract benefits on the date that services are rendered. Contract language, including definitions and specific inclusions/ exclusions, as well as state and federal law, must be considered in determining eligibility for coverage. Members must consult their applicable benefit plans or contact a Member Services representative for specific coverage information. Likewise, medical policy, which addresses the issue(s) in any specific case, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving and the Company reserves the right to review and update medical policy periodically.

### Tumor Treating Fields Therapy

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>With newly diagnosed glioblastoma multiforme on maintenance therapy after initial treatment</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Tumor treating fields therapy as an adjunct to standard maintenance therapy</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Standard maintenance therapy alone</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>Overall survival</li> <li>Disease-specific survival</li> <li>Quality of life</li> <li>Treatment-related morbidity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>With progressive or recurrent glioblastoma multiforme</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Tumor treating fields therapy as an adjunct or alternative to medical therapy</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Standard medical therapy</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>Overall survival</li> <li>Disease-specific survival</li> <li>Quality of life</li> <li>Treatment-related morbidity</li> </ul>

#### Summary

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes a randomized controlled trial (RCT). Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.



For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

## OBJECTIVE

The objective of this evidence review is to determine whether the use of tumor treating fields therapy improves the net health outcome for patients with solid tumors including glioblastoma multiforme.

## POLICY

Tumor treating fields therapy to treat glioblastoma multiforme is considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

- Adult patients ≥18 years of age
- Supratentorial tumor
- Karnofsky Performance Status score ≥70%
- Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (see Policy Guidelines).

Tumor treating fields therapy is considered **investigational** in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (eg, bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
- For brain metastases
- For cancer in areas other than the brain.

## POLICY GUIDELINES

Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth >25% compared with the smallest tumor area measured in the patient during the trial or appearance of 1 or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).

The Food and Drug Administration label includes the following notices:

- Patients should use Optune for at least 18 hours a day to get the best response to treatment
- Patients should finish at least 4 full weeks of therapy to get the best response to treatment. Stopping treatment before 4 weeks lowers the chances of a response to treatment.

There are no specific codes for the initial application of this system or instruction on use. The patient reapplies the transducer arrays at home after the initial instruction.

There are HCPCS codes for the system and the transducer arrays:

E0766 Electrical stimulation device, used for cancer treatment, includes all accessories, any type

A4555 Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only.

## BENEFIT APPLICATION

### BlueCard/National Account Issues

State or federal mandates (eg, Federal Employee Program) may dictate that certain U.S. Food and Drug Administration–approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only on the basis of their medical necessity.

## BACKGROUND

### Glioblastoma Multiforme



Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.<sup>1</sup> GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (eg, bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors.<sup>1</sup> The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to 1 year, and the 5-year survival rate was around 5%.<sup>2</sup>

### **Clinical Context and Therapy Purpose**

The purpose of alternating electrical field therapy, more commonly known as tumor treating fields (TTF) therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

### **Treatment of Newly Diagnosed GBM**

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these 2 therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival rates with temozolomide are higher in patients who have O<sup>6</sup>-methylguanine-DNA methyltransferase (*MGMT*) gene promoter methylation (see 2.04.113 on *MGMT* promoter methylation for malignant gliomas).

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice (see the Supplemental Information section).<sup>3</sup> For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially all patients.

### **Treatment of Recurrent GBM**

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (eg, lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%.<sup>4</sup> There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

The questions addressed in this evidence review are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

### **Patients**

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

### **Interventions**

TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields.<sup>4-6</sup> TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. TTF therapy is proposed to inhibit tumor growth by 2 mechanisms:

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the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase.<sup>5,6</sup> Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune (formerly NovoTTF-100A System) is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

### **Comparators**

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

The following practices are currently being used to make decisions about recurrent GBM: medical therapy.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months.<sup>4</sup>

### **Outcomes**

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

### **Timing**

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

### **Setting**

The setting is outpatient care by an oncologist or neuro-oncologist.

### **Regulatory Status**

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.<sup>7</sup> The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved Novocure's request for a product name change from NovoTTF-110A System to Optune®.<sup>8</sup>

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.<sup>9</sup> The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

FDA product code: NZK.

### **RATIONALE**

This evidence review was created in August 2013 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through April 5, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.



To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

For this review, 3 indications are evaluated: (1) tumor treating fields (TTF) as an adjunct to maintenance chemotherapy in newly diagnosed patients following initial treatment with surgery, radiotherapy and chemotherapy and (2) TTF as an adjunct or (3) alternative to medical therapy (eg, bevacizumab, chemotherapy) in progressive or recurrent glioblastoma multiforme (GBM).

### Study Selection

The PICOTS was used to select relevant studies.

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Within each category of study design, studies with larger sample size studies and longer duration were sought.

## TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM

### Randomized Controlled Trials

Stupp et al (2017) published results of the EF-14 multicenter, open-label phase 3 RCT that evaluated maintenance therapy with TTF for newly diagnosed GBM.<sup>10</sup> The trial included 695 patients from 83 sites who had supratentorial GBM and had completed standard treatment consisting of biopsy or surgical resection followed by radiotherapy and chemotherapy (see Table 1). A Karnofsky Performance Status (KPS) score of 70 or higher was an additional inclusion criterion to ensure independence in activities of daily living, and patients with rapidly progressing GBM following radiochemotherapy were excluded from the trial. Patients were randomized in a 2:1 fashion to TTF plus maintenance temozolomide or maintenance temozolomide alone.

All patients were seen monthly for follow-up. Quality of life (QOL) was assessed every 3 months, and magnetic resonance imaging (MRI) was performed every 2 months until tumor progression. Tumor progression on MRI was adjudicated by a central review committee blinded to treatment group. The primary outcome was progression-free survival (PFS), and the secondary outcome was overall survival (OS). The analysis was by intention-to-treat, including 26 patients from the control arm who crossed over to TTF following the planned interim analysis.

In 2014, an independent data and safety monitoring board concluded from the planned interim analysis that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended trial termination. The Food and Drug Administration approved the trial termination, and the trial was closed to recruitment with 695 of the planned 700 participants randomized. Control arm participants were allowed to cross over to the experimental treatment at this time. The interim analysis, which the Food and Drug Administration considered for the 2015 expanded approval of Optune, was published by Stupp et al (2015).<sup>11</sup> At the time of the interim analysis, data were available for 210 patients randomized to TTF plus temozolomide and 105 patients to temozolomide alone. Follow-up of the remainder of the 695 enrolled patients continued after enrollment was closed.

**Table 1. Key Randomized Controlled Trial Characteristics for Newly Diagnosed Glioblastoma**

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Stupp et al (2017) <sup>10</sup> ; EF-14	U.S., E.U., South Korea, Israel	83	2009-2016	<ul style="list-style-type: none"> <li>• 695 newly diagnosed with GBM and treated by radiochemotherapy</li> <li>• KPS score <math>\geq 70</math></li> </ul>	TTF >18 h/d plus maintenance temozolomide (n=466)	Maintenance temozolomide alone (5 d every 28 d for 6 cycles) (n=229)

GBM: glioblastoma multiforme; h/d; hours per day; KPS: Karnofsky Performance Status; TTF: tumor treatment fields.

Results of the final analysis of the EF-14 trial were similar to the interim analysis and are shown in Table 2. Both PFS and OS improved with the addition of TTF therapy to standard maintenance chemotherapy (ie, temozolomide). PFS increased by 2.7 mo ( $p < 0.001$ ) and OS increased by 4.9 mo ( $p < 0.001$ ) in the TTF group. The time to a decrease in mental function was 2.5 months longer with TTF therapy ( $p < 0.01$ ).

There was a similar percentage of dropouts at the final analysis—with 49 (11%) patients in the TTF group and 27 (12%) patients in the temozolomide alone group. More treatment cycles with temozolomide were administered in the TTF group (median, 6 for TTF group vs 5 for controls), a finding that is consistent with the longer PFS. Rates of adverse events were similar between the groups, including rates of seizures. In secondary analysis of patients who had not progressed, there



was no reduction in health-related quality of life with TTF compared with temozolomide alone aside from “itchy skin”.<sup>12</sup> Interpretation of this result is limited by the low percentage of patients who completed the health-related quality of life assessments at follow-up (65.8% of the 655 patients alive at 3 months and 41.7% of the 473 patients alive at 12 months). A mixed-model analysis, which accounts for missing data, confirmed the results of the mean change from baseline analysis.

**Table 2. Key Randomized Controlled Trial Results for Newly Diagnosed Glioblastoma**

Study	Final N (%)	Median PFS (95% CI), mo	Median OS (95% CI), mo	Systemic Adverse Events, n (%)	Seizures, n (%)	Time to 6-Point Decline in MMSE Score (95% CI), mo
Stupp et al (2017) <sup>10</sup>						
TTF + temozolomide	417 (89)	6.7 (6.1 to 8.1)	20.9 (19.3 to 22.7)	218 (48)	26 (6)	16.7 (14.7 to 19.0)
Temozolomide alone	202 (88)	4.0 (3.8 to 4.4)	16.0 (14.0 to 18.4)	94 (44)	13 (6)	14.2 (12.7 to 17.0)
HR (95% CI)		0.63 (0.52 to 0.76)	0.63 (0.53 to 0.76)			0.79 (0.66 to 0.95)
P value		<0.001	<0.001	0.58		0.01

CI: confidence interval; HR: hazard ratio; MMSE: Mini-Mental State Examination; OS: overall survival; PFS: progression-free survival; TTF: tumor treatment fields.

Tables 3 and 4 display notable gaps identified in this trial, the major limitation is the lack of patient blinding to treatment assignment. However, PFS was assessed by investigators who were blinded to treatment and placebo effects on OS were expected to be minimal. Investigators considered it practically unfeasible (due to the heat and current of the TTF therapy) and ethically unacceptable to submit the control patients to repeated shaving of the head and continuous wear of a sham device over many months.

**Table 3. Relevance Gaps**

Study; Trial	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Stupp et al (2017) <sup>10</sup> ; EF-14			3. Possible differences in post-progression treatment affecting overall survival		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 4. Study Design and Conduct Gaps**

Study; Trial	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
Stupp et al (2017) <sup>10</sup> ; EF-14		1. No sham control and not blinded to treatment assignment				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

### Section Summary: TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM

The final analysis of the EF-14 trial, which included 695 patients from 83 sites, found a statistically and clinically significant increase of 2.7 months in PFS and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. There was no sham control, and patients were not blinded to treatment assignment, but PFS was assessed by blinded evaluators, and placebo effects on the



objective measure of OS were likely to be minimal. There was no evidence of a negative impact of TTF therapy on health-related quality of life, except for itchy skin from the transducers.

## TTF Therapy as an Adjunct or Alternative to Medical Therapy for Progressive or Recurrent GBM

### Randomized Controlled Trials

The 2011 Food and Drug Administration approval of the NovoTTF-100A System (now called Optune) was based on a phase 3 multinational RCT (EF-11), results of which were published by Stupp et al (2012).<sup>4</sup> This trial compared TTF therapy alone with physician's choice medical therapy in 237 adults who had relapsed or progressive glioblastoma (see Table 5). Patients had failed conventional treatment with radiotherapy, chemotherapy, and/or surgery, and more than 80% of participants had failed 2 or more prior chemotherapy regimens. In this trial, the term chemotherapy also applied to targeted agents such as bevacizumab. Patient characteristics and performance of additional post-recurrence debulking surgery were similar in the 2 groups.

**Table 5. Summary of Key Randomized Controlled Trial Characteristics for Progressive or Recurrent Glioblastoma**

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Stupp et al (2012) <sup>4</sup> ; EF-11	U.S., E.U., Israel	28	1987-2013	<ul style="list-style-type: none"> <li>237 adults with relapsed or progressive supratentorial glioblastoma</li> <li>KPS score <math>\geq 70\%</math></li> </ul>	120 patients treated with TTF alone, 93 (78%) completed 1 cycle	117 patients treated with physician's choice of medical therapy <sup>a</sup>

EU: European Union; KPS: Karnofsky Performance Status; TTF: tumor treating fields.

<sup>a</sup> Medical therapy included bevacizumab, irinotecan, nitrosoureas, platinum-based chemotherapy (ie, carboplatin); temozolomide; or a combination of procarbazine, chloroethyl ether, and vincristine.

Participants were followed monthly, including laboratory tests. MRI images were evaluated at 2, 4, and 6 months from initiation of treatment, with subsequent MRIs performed according to local practice until disease progression. QOL questionnaires were completed every 3 months. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess mortality rates. The primary end point was OS. Secondary end points included PFS, the percentage of patients with PFS at 6 months, time to progression, 1-year survival rate, QOL, and radiologic response. All end points were evaluated using intention-to-treat analysis.

The trial did not reach its primary end point of improved survival compared with active medical therapy (see Table 6). With a median follow-up of 39 months, 93% of patients had died. There was not a statistically significant difference in survival rates at 1, 2, and 3 years between groups. Patients in the TTF group did not, however, suffer the typical systemic side effects of chemotherapy. The most common adverse event in the TTF group was grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids and did not require treatment breaks. Control participants experienced grade 2, 3, or 4 events by organ system related to the pharmacologic activity of chemotherapy agents used. Hematologic events of grade 2 or greater were observed in 17% of chemotherapy patients compared with 3% of TTF patients. Gastrointestinal disorders of grade 2 or greater were identified in 17% of chemotherapy patients compared with 4% of TTF patients. Severe (grades 3-4) hematologic and gastrointestinal toxicity was observed in 7% of chemotherapy controls compared with 1% of the TTF group.

Longitudinal QOL data, available in 63 (27%) participants, showed no meaningful differences between groups for the domains of global health and social functioning. However, cognitive and emotional functioning domains favored TTF therapy. Symptom scale analysis was by treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.

The trial had a number of limitations (see Tables 7 and 8), that included lack of blinding and high loss to follow-up. Discontinuation of TTF therapy occurred in 22% of patients due to noncompliance or inability to handle the device, usually within the first few days. In the control group, 21 (18%) patients did not return to the treatment site, and details on disease progression and toxicity were not available. Longitudinal QOL could be analyzed only for 27% of patients who remained on study therapy for 3 months. The trial was designed as a superiority trial and did not provide adequate evidence of noninferiority.

**Table 6. Summary of Key Randomized Controlled Trial Results for Recurrent or Progressive Glioblastoma**

Study; Trial	LTFU, n (%)	Median OS, mo	Progression-Free Survival		Overall Survival (95% CI), %		
			Median, mo	Rate at 6 Months (95% CI), %	1 Year	2 Years	3 Years
Stupp et al (2012) <sup>4</sup> ; EF-11 TTF	23 (22)	6.6	2.2	21.4 (13.5 to 29.3)	20	8 (4 to 13)	4 (1 to 8)
PCC HR (95% CI)	12 (18)	6.0	2.1	15.1 (7.8 to 22.3)	20	5 (3 to 10)	1 (0 to 3)
		0.86 (0.66 to 1.12)	0.81 (0.60 to 1.09)				



P value

0.27

0.16

0.13

CI: confidence interval; HR: hazard ratio; LTFU: loss to follow-up; PCC: physician's choice chemotherapy; TTF: tumor treating fields.

**Table 7. Relevance Gaps**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Stupp et al (2012) <sup>4</sup> ; EF-11			2. Physician's choice chemotherapy		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 8. Study Design and Conduct Gaps**

Study; Trial	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>d</sup>	Data Completeness <sup>e</sup>	Power <sup>d</sup>	Statistical <sup>f</sup>
Stupp et al (2012) <sup>4</sup> ; EF-11		1. Not blinded to treatment assignment		1. 78% of TTF group completed only 1 cycle of therapy, 18% of control group lost to follow-up 1. Longitudinal QOL data were available for 27% of patients		1. Not designed as a noninferiority trial

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.  
QOL: quality of life.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

## Nonrandomized Comparative Studies

Kesari et al (2017) conducted a post hoc analysis of the EF-14 trial (see Stupp et al [2017] above) to evaluate the efficacy of TTF in patients who had the first recurrence.<sup>13</sup> Some patients in the temozolomide alone group crossed over to receive TTF plus chemotherapy after the first recurrence, resulting in 144 patients who received TTF fields plus chemotherapy and 60 patients who received chemotherapy alone for recurrent GBM (see Table 9). Patient characteristics and second-line treatments were well-balanced between the groups, with bevacizumab the most common second-line therapy. The median OS in patients treated with systemic therapy alone was 9.2 months (see Table 10). In comparison, the group of patients who received TTF therapy in addition to systemic therapy had a median OS of 11.8 months (p=0.043).

A registry study published Mrugala et al (2014) assessed OS data from patients who received NovoTTF therapy in a real-world, clinical practice setting (see Table 9).<sup>14</sup> Concurrent treatment was not captured in the registry, and it is possible that some patients received combination therapy. Median OS in the PRiDe clinical practice dataset (9.6 mo) was reported as superior to that attained in the EF-11 pivotal trial (6.6 mo, p<0.001) (see Table 10). More patients in the PRiDe registry were treated for first recurrence (33% vs 9%), and more had received bevacizumab as prior therapy (55% vs 19%). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

**Table 9. Characteristics of Key Nonrandomized Trial Results**

Study	Study Type	Country	Dates	Participants	TTF	Controls	FU
Kesari et al (2017) <sup>13</sup>	EF-14 post hoc analysis	U.S., E.U., South Korea, Israel	2009-2016	204 patients with first recurrence in the EF-14 trial	144 patients treated with TTF plus second-line chemotherapy	60 patients treated with second-line chemotherapy	12.6 mo
Mrugala et al (2014) <sup>14</sup>	Registry	U.S. (91 centers)	2011-2013	457 patients with recurrent GBM	Patient Registry Dataset (PRiDe)	EF-11	

FU: follow-up; GBM: glioblastoma; TTF: tumor treating fields.

**Table 10. Summary of Key Nonrandomized Trial Results**

Study	Median OS, mo	Median OS With Bevacizumab, mo
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Case 1:20-cv-00194-WCG Filed 04/28/20 Page 385 of 1212 Document 11-2 1864



Kesari et al (2017) <sup>13</sup> ; EF-14			
TTF plus chemotherapy	11.8	11.8	
Chemotherapy alone	9.2	9.0	
Hazard ratio (95% CI)	0.70 (0.48 to 1.00)	0.61 (0.37 to 0.99)	
P value	0.049	0.043	
		<b>1-Year OS, %</b>	<b>2-Year OS, %</b>
Mrugala et al (2014) <sup>14</sup>			
PRIDe Registry	9.6	44	30
EF-11	6.6	20	9
Hazard ratio (95% CI)	0.66 (0.05 to 0.86)		
P value	<0.001		

CI: confidence interval; OS: overall survival, TTF: tumor treating fields.

Post hoc analyses of the EF-11 pivotal trial have been reported. Wong et al (2014) published a subgroup analysis to determine characteristics of responders and nonresponders in the active treatment and active treatment control.<sup>15</sup> They found that responders had a lower grade of histology and lower daily dexamethasone use than nonresponders. A second post hoc analysis by Kanner et al (2014) of the EF-11 pivotal trial data was performed to evaluate OS among patients who finished at least 1 complete course of TTF or chemotherapy.<sup>16</sup> The investigators reported that median OS was 7.7 months in the TTF group compared with 5.9 months in the chemotherapy group ( $p=0.009$ ). These post hoc analyses are considered to be hypothesis-generating.

### Section Summary: TTF Therapy as an Adjunct or Alternative to Chemotherapy for Progressive or Recurrent GBM

The single RCT for TTF as an alternative to chemotherapy reported that outcomes following TTF therapy were similar to outcomes following standard chemotherapy. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. The noninferiority of TTF compared with chemotherapy might be considered a sufficient health benefit, if TTF reduced treatment toxicity. However, because the trial was not designed as a noninferiority trial no inferences of noninferiority compared with chemotherapy can be made. Physician's choice therapy during the trial was heterogeneous, although analysis indicated that survival was not affected by choice of chemotherapy. More patients in the TTF group than in the control group did not complete the treatment course. The number of patients who contributed QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators might have been subject to bias due to the lack of blinding.

A nonrandomized post hoc evaluation of the EF-14 trial suggests that TTF may improve survival when combined with chemotherapy for recurrent GBM. This analysis should be considered hypothesis-generating, and further study in high-quality RCTs is needed.

### Summary of Evidence

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes an RCT. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

### SUPPLEMENTAL INFORMATION

#### Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.



In response to requests, input was received from 3 physician specialty societies (one of which provided 6 responses and 2 of which provided 1 response each) and 1 academic medical center (total of 9 individual responses) while this policy was under review in 2016. There was majority support, but not consensus, for the use of tumor treatment fields therapy as an adjunct to maintenance treatment following initial therapy for glioblastoma multiforme. There was mixed support for the use of tumor treatment fields as an alternative to chemotherapy in advanced or recurrent glioblastoma multiforme.

### Practice Guidelines and Position Statements

National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2018) include recommendations for the treatment of glioblastoma (see Table 11).<sup>3</sup> For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate O<sup>6</sup>-methylguanine-DNA methyltransferase promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric field therapy is a category 1 recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a category 2B recommendation.

**Table 11. Guidelines for Adjuvant Treatment of Glioblastoma, by Age and Performance Status**

Age, y	KPS Score, %	Treatment Options	Category
≤70	≥60	<ul style="list-style-type: none"> <li>Standard RT plus concurrent and adjuvant temozolomide plus TTF</li> <li>Standard RT plus concurrent and adjuvant temozolomide</li> </ul>	1
≤70	<60	<ul style="list-style-type: none"> <li>Hypofractionated RT with/without concurrent or adjuvant temozolomide</li> <li>Temozolomide</li> <li>Palliative/best supportive care</li> </ul>	2A
>70	≥60	<ul style="list-style-type: none"> <li>Hypofractionated RT plus concurrent and adjuvant temozolomide</li> <li>Standard RT plus concurrent and adjuvant temozolomide plus TTF</li> <li>Temozolomide alone</li> </ul>	1
>70	<60	<ul style="list-style-type: none"> <li>Hypofractionated brain RT alone</li> <li>Hypofractionated brain RT alone</li> <li>Temozolomide alone</li> <li>Palliative/best supportive care</li> </ul>	2A

KPS: Karnofsky Performance Status; RT: radiotherapy; TTF: tumor treating fields.

### U.S. Preventive Services Task Force Recommendations

Not applicable.

### Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

### Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 12. Of particular note are the phase 3 trials evaluating TTF therapy in non-small-cell lung cancer and pancreatic cancer. TTF therapy is an active area of research for mechanisms underlying its effects on cancer cells.

**Table 12. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
NCT01971281 <sup>a</sup>	A Phase II Study of TTFields (150 kHz) Concomitant With Gemcitabine and TTFields Concomitant With Gemcitabine Plus Nab-paclitaxel for Front-line Therapy of Advanced Pancreatic Adenocarcinoma	40	Dec 2017 (ongoing)
NCT01894061 <sup>a</sup>	A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma	40	Dec 2018
NCT02663271 <sup>a</sup>	A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFields and Pulsed Bevacizumab Treatment in Patients With Bevacizumab-refractory Recurrent Glioblastoma	18	Mar 2019
NCT02831959 <sup>a</sup>	Pivotal, Open-label, Randomized Study of Radiosurgery With or Without Tumor Treating Fields (TTFields) (150kHz) for 1-10 Brain Metastases From Non-small Cell Lung Cancer (NSCLC) (METIS)	270	Jul 2019
NCT02973789 <sup>a</sup>	LUNAR: Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields) Concurrent With Standard of Care Therapies for Treatment of Stage 4 Non-small Cell Lung Cancer (NSCLC) Following Platinum Failure	534	Dec 2021
NCT02743078 <sup>a</sup>	Phase II Trial Of Optune® Plus Bevacizumab In Bevacizumab-Refractory Recurrent Glioblastoma	85	Aug 2022



NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03377491 <sup>a</sup>	EF-27 Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields, 150kHz) Concomitant With Gemcitabine and Nab-paclitaxel for Front-line Treatment of Locally-advanced Pancreatic Adenocarcinoma (PANOVA-3)	556	Dec 2022

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

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## CODES

Codes	Number	Description
CPT		No specific code – See Policy Guidelines
	191.0-191.9	Malignant neoplasm of brain code range
HCPCS	A4555	Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only
	E0766	Electrical stimulation device, used for cancer treatment, includes all accessories, any type
ICD-10-CM		Investigational for all relevant diagnoses
	C71.0-C71.9	Malignant neoplasm of brain code range
ICD-10-PCS		Not applicable. Policy is only for outpatient services. ICD-10-PCS codes are only used for inpatient services
Type of Service		
Place of Service		

Posted on: 08/17/2018



# TUMOR-TREATMENT FIELDS THERAPY FOR GLIOBLASTOMA (REQUIRES PREAUTHORIZATION) VIII.9

## DESCRIPTION

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults. They comprise approximately 15% of all brain and central nervous system tumors, and more than 50% of all tumors that arise from glial cells. The peak incidence for GBM occurs between the ages of 45 and 70 years. GBMs are grade IV astrocytoma and are often resistant to standard chemotherapy. According to the National Comprehensive Cancer Network, GBM is the "deadliest brain tumor with only a third of patients surviving for 1 year and less than 5% living beyond 5 years.

Alternating electric fields, generated by insulated electrodes, have been reported to exhibit inhibitory effect on the growth rate of variety of human and rodent tumor cell lines as well as malignant tumors in animals. This non-thermal effect selectively affects dividing cells while quiescent cells are left intact.

## DATES

Original Effective

**07-20-2016**

Last Review

**11-08-2017**

Next Review

**11-30-2018**

## POLICY

I. Tumor treatment fields therapy may be considered **medically necessary** as combination therapy for glioblastoma when **ALL** of the following are met:

- A. the member is 18 years of age or older **AND**
- B. the member is newly diagnosed with supratentorial, histologically confirmed glioblastoma **AND**
- C. will be used with temozolomide (TMZ) following initial treatment with surgery, chemotherapy or radiation.



8/13/2018  
II. Tumor treatment fields therapy may be considered **medically necessary** as monotherapy for glioblastoma when **ALL** of the following are met:

- A. the member is 18 years of age or older **AND**
- B. the member has recurrence of supratentorial, histologically confirmed glioblastoma **AND**
- C. following initial treatment with chemotherapy or radiation

III. Tumor treatment fields therapy for all other indications is considered **investigational** as the clinical effectiveness has not been established.

## BACKGROUND

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults. They comprise approximately 15% of all brain and central nervous system tumors and more than 50% of all tumors that arise from glial cells.<sup>1</sup> The peak incidence for GBM occurs between the ages of 45 and 70 years. GBMs are grade IV astrocytomas, the most deadly type of glial cell tumor, and are often resistant to standard chemotherapy.<sup>1</sup> According to the National Comprehensive Cancer Network, GBM is the "deadliest brain tumor with only a third of patients surviving for 1 year and less than 5% living beyond 5 years."<sup>2</sup>

The primary treatment for GBM is debulking surgery to remove as much of the tumor as possible. At that time, some patients may undergo implantation of the tumor cavity with a carmustine (bischloroethylnitrosourea [BCNU])?impregnated wafer.<sup>2</sup> Depending on the patient's physical condition, adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of the 2 are sometimes given. After adjuvant therapy, some patients may undergo maintenance therapy with temozolomide.

No standard treatment exists for recurrent GBM. In patients with disease that recurs after these initial therapies, additional debulking surgery may be used if recurrence is localized. Other treatment options for recurrent disease include various forms of systemic medications such as bevacizumab, bevacizumab plus chemotherapy (eg, irinotecan, BCNU/chloroethylnitrosourea [CCNU], temozolomide), temozolomide, nitrosourea, PCV (procarbazine, CCNU, vincristine), cyclophosphamide, and platinum-based agents.<sup>2</sup> External beam radiotherapy (EBRT) also may be used to treat recurrent GBM. Response rates in recurrent disease are less than 10%, and progression-free survival rates at 6 months are less than 20%.<sup>2,3</sup>

TTF therapy is a new, noninvasive technology that is intended to treat GBM on an outpatient basis using electrical fields.<sup>3-5</sup> TTF therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis. TTF are proposed to inhibit rapidly dividing tumor cells by 2 mechanisms, arrest of cell proliferation and destruction of cells while undergoing division.<sup>4,5</sup>

The NovoTTF-100A™ System (Novocure, Haifa, Israel) has received FDA marketing approval to deliver TTF therapy. TTF therapy via the NovoTTF-100A™ System is delivered by a battery-powered, portable device that generates the fields via disposable electrodes that are noninvasively attached to the patient's shaved scalp over the site of the



tumor.<sup>3,4</sup> The device is used by the patient at home on a continuous basis (20-24 h/d) for the duration of treatment, which can last for several months. Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living.<sup>3,4</sup>

## RATIONALE

This evidence review was created in August 2013 and updated periodically through literature reviews, most recently through July 8, 2015. No new studies were identified that would change the conclusions of the evidence review. Following is a summary of the key literature.

### Randomized Controlled Trials

The U.S. Food and Drug Administration (FDA) approval of the NovoTTF-100A system was based on a phase 3, multinational prospective randomized controlled trial (RCT) (EF11) which was published in 2012 by Stupp et al. The Stupp study, which was sponsored and funded by the manufacturer of the device (Novocure), compared tumor-treatment fields (TTF) therapy (delivered by the NovoTTF-100A System) with the best standard of care chemotherapy (active control).<sup>3</sup> Twenty-eight clinical centers (across 7 countries) enrolled 237 adult participants with relapsed or progressive glioblastoma multiforme (GBM), despite conventional radiotherapy. Other prior treatments may have included surgery and/or chemotherapy. Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky Performance Status score of 80%. More than 80% of participants had failed 2 or more prior chemotherapy regimens ( $\geq$  second recurrence), and 20% had failed bevacizumab before study enrollment.

Two hundred thirty-seven patients were randomized in a 1:1 ratio to receive TTF therapy only (n=120) or active control (n=117). The choice of chemotherapy regimens varied, reflecting local practice at each of the participating clinical centers. Chemotherapy agents considered as active control during the trial included platinum-based chemotherapy (ie, carboplatin); nitrosoureas; procarbazine; combination of procarbazine, lomustine and vincristine (PCV); temozolomide; and bevacizumab. For patients assigned to the TTF group, uninterrupted treatment was recommended, although patients were allowed to take treatment breaks of up to 1 hour, twice per day, for personal needs (eg, shower). In addition, patients assigned to the TTF group were allowed to take 2 to 3 days off treatment at the end of each of 4-week period (which is the minimal required treatment duration for TTF therapy to reverse tumor growth). A period of 28 days of treatment with TTF was considered 1 full treatment course.

The primary study end point in this RCT was overall survival (OS).<sup>3</sup> Secondary end points included progression-free survival (PFS) at 6 months, TTP, 1-year survival rate, quality of life (QOL), and radiologic response. Participants were seen in clinic monthly, and magnetic resonance imaging (MRI) was performed after 2, 4, and 6 months from initiation of treatment, with subsequent MRI done according to local practice until disease progression. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess participant mortality rates.

Ninety-seven percent (116) of 120 participants in the TTF group started treatment and 93 participants (78%) completed 1 cycle (4 weeks) of therapy. Discontinuation of TTF therapy occurred in 27 participants (22%) due to noncompliance or the inability to handle the device.<sup>3</sup> For each TTF treatment month, the median compliance was 86% (range, 41%-98%), which equaled a mean use of 20.6 hours per day. In the active control group, 113 (97%)



of the 117 assigned participants received chemotherapy and all except 1 individual completed a full treatment course. Twenty-one participants (18%) in the active control group did not return to the treating site and details on disease progression and toxicity were not available.

This RCT did not reach its primary end point of improved survival compared with active chemotherapy. With a median follow-up of 39 months, 220 participants (93%) had died. Median survival was 6.6 months in the TTF group compared with 6.0 months in the active control group (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.66 to 1.12;  $p=0.27$ ). For both groups, 1-year survival was 20%. The survival rates for 2- and 3-year survival were 8% and 4%, respectively, for the TTF group versus 5% and 1%, respectively, for the active control group. PFS rate at 6 months was 21.4% in the TTF group, compared with 15.1% in the active control group ( $p=0.13$ ). Objective radiologic responses (partial and complete response) were noted in 14 participants in the TTF group and 7 in the active control group, with a calculated response rate of 14.0% (95% CI, 7.9% to 22.4%) versus 9.6% (95% CI, 3.9% to 18.8%), respectively. Sixteen percent of the TTF participants had grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids. Active control participants experienced grade 2 to 4 events by organ system related to the pharmacologic activity of chemotherapy agents used; severe (grades 3 and 4) toxicity was observed in 3% of participants.

Longitudinal QOL data were available in 63 participants (27%). There were no meaningful differences observed between the groups in the domains of global health and social functioning. However, cognitive, emotional, and role functioning favored TTF therapy, whereas physical functioning favored chemotherapy. Symptom scale analysis was in accordance to treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the TTF group.

In summary, this RCT failed to demonstrate the primary end point of improved survival with TTF therapy in comparison with chemotherapy.<sup>3,9</sup> Limitations of the trial included a somewhat heterogeneous patient population, with participants included after progression of 1 or several lines of chemotherapy, as well as the use of different chemotherapy regimens in the control group. Another limitation is the absence of a placebo/supportive care arm. In the setting of advanced disease, the supportive care arm would have been useful to gauge the safety and efficacy of treatment for both groups of patients. Treatments used in the active control arm (best standard of care chemotherapy) in the recurrent disease setting have previously demonstrated limited efficacy, thus limiting the ability to determine the true treatment effect of TTF. Data from a trial of TTF versus placebo, or TTF plus standard chemotherapy versus standard chemotherapy alone would therefore provide a better assessment of treatment efficacy. The latter study design is being used in an ongoing trial of TTF therapy in the treatment of patients with newly diagnosed GBM (see Ongoing and Unpublished Clinical Trials section).

A further limitation was high dropout rates in both groups. For example, over 20% of participants in the active control group were lost at follow-up, and this degree of the number of dropouts may have underestimated the toxicity evaluation in this group. Similarly, over 20% of participants in the TTF arm discontinued treatment within a few days due to noncompliance or inability to handle the device. This implies that compliance might be an issue with TTF, because it requires the patient to continuously wear transducers on the shaved head. Finally, the number of patients who completed the QOL data was approximately one quarter of total enrollment, and the self-reported QOL indicators may have been subject to bias due to the lack of blinding.<sup>3,6</sup>

Wong et al published a subgroup analysis of the previously described RCT to determine characteristics of responders and nonresponders in the treatment and active control groups.<sup>10</sup> Tumor response was assessed by the Macdonald criteria. More patients in the TTF arm were considered responders (14/120 vs 7/117 in the chemotherapy arm.) Median response time was longer for those in the TTF arm than the chemotherapy arm (7.3 months vs 5.6 months,  $p=0.001$ ), and the overall survival was longer in the TTF arm (12.1 months vs 10.5 months,  $p=0.001$ ).<sup>10</sup>



TTF arm ( $p < 0.001$ ) but not in the chemotherapy arm ( $p = 0.29$ ). Compared with the chemotherapy arm, a higher proportion of responders in the TTF arm had a prior lowgrade histology (36% vs 0%). These differences in treatment responder groups suggest that TTF therapy may differentially benefit certain types of GBM; however, the small numbers of responders in both groups limits generalizations that can be drawn from this analysis.

A second post hoc analysis of the TTF EF-11 pivotal trial data was performed to evaluate OS rates among patients who completed at least 1 complete course of TTF or chemotherapy.<sup>11</sup> These investigators analyzed survival in what they referred to as a “modified ITT [intention-to-treat]” subgroup comprising 93 of 120 (78%) of the original TTF allocated group, versus 117 of 117 (100%) of the original chemotherapy allocated group. This exercise revealed median OS of 7.7 months in the TTF modified ITT (mITT) group compared with 5.9 months in the chemotherapy group (HR=0.69; 95% CI, 0.52 to 0.91;  $p = 0.009$ ). They also showed a trend relationship between proportion of patients with higher TTF compliance and median OS rates ( $p = 0.039$ ). The investigators suggest that TTF provides an OS benefit if used as intended in the FDA-approved label when compared with best chemotherapy. This post hoc analysis is limited as it was not prespecified in the study, includes only 78% of the original TTF allocated patients, and fails to control for noncompliance due to faster clinical deterioration of TTF recipients leading to treatment cessation.

## Noncomparative Studies

A study published in late 2014 included OS data from 457 patients included in the Patient Registry Dataset (PRiDe), a postmarketing registry of all recurrent GBM patients who received NovoTTF therapy in a real-world, clinical practice setting in 91 centers in the United States between October 2011 and November 2013.<sup>12</sup> The median OS rate in the PRiDe clinical practice dataset was reported as significantly superior to that attained in the TTF EF-11 pivotal trial (9.6 months vs 6.6 months; HR=0.66, 95% CI, 0.05 to 0.86;  $p < 0.001$ ). One- and 2-year OS rates for TTF in PRiDe were significantly longer than those in the TTF group in the EF-11 trial (44% vs 20% at 1 year; 30% vs 9% at 2 years, respectively). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

The use of TTF and the corresponding effects on living tissue have been evaluated in uncontrolled studies in a number of clinical settings.<sup>13-15</sup> Kirson et al (2007), for example, reported the findings of a case study examining the effects of TTF therapy delivered by the NovoTTF-100A System in 10 patients with recurrent GBM.<sup>13</sup> Median time to progression (TTP) in these patients was 26.1 weeks, and median OS was 62.2 weeks. The authors noted that these TTP and OS values were more than double the reported medians of historical control patients. No device-related serious adverse events were seen after more than 70 months of cumulative treatment in all of the patients. The only device-related adverse event observed was a mild-to-moderate contact dermatitis beneath the field delivering electrodes. The primary limitation of this study was the use of historical controls, because the patients included may not be comparable on major clinical and prognostic features.<sup>13</sup>

Two small case series have been published of long-term survival (>6 years) with TTF therapy.<sup>16,17</sup> Rulseh et al reported long-term (>7 year) survival in 4 of 20 patients with GBM who were treated with TTF,<sup>16</sup> while Villano et al describe 1 patient with recurrent GBM who was tumor-free more than 6 years after treatment with TTF.<sup>17</sup>

Since the approval of the NovoTTF device, additional case reports and small case series have been reported. Elzinga and Wong reported a case of a patient who demonstrated improved tumor response to bevacizumab in a patient who also received TTF therapy.<sup>18</sup> Another case series ( $n = 3$ ) suggested that adjusting the size of the electric fields may improve response in cases of local tumor progression.<sup>19</sup>

## Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.



**Table 1. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment Date	Completion
<b>Ongoing</b>			
NCT00916409 <sup>a</sup>	A Prospective, Multi-center Trial of NovoTTF-100A Together with Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM	700	Jul 2016
NCT01894061 <sup>a</sup>	A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma	40	Oct 2016
NCT01755624 <sup>a</sup>	A Phase II Randomized Study of TTField Therapy Versus Supportive Care in Non-small Cell Lung Cancer Patients With 1-5 Brain Metastases Following Optimal Standard Local Treatment	60	Jul 2017
NCT01756729 <sup>a</sup>	A Prospective, Non-randomized, Concurrent Control, Open Label, Post-approval Study of NovoTTF-100A in Recurrent GBM Patient	486	Jan 2018
NCT01954576	A Phase II Study of the NovoTTF-100A system, Enhanced by Genomic Analysis to Identify the Genetic Signature of Response in the Treatment of Recurrent Glioblastoma Multiforme	30	May 2018

NCT: national clinical trial. <sup>a</sup> Denotes industry-sponsored or cosponsored trial.

## Summary of Evidence

The evidence for tumor-treatment fields therapy in patients who have recurrent glioblastoma multiforme includes 1 randomized controlled superiority pivotal trial using the U.S. Food and Drug Administration? approved device and a number of small observational studies. Relevant outcomes include overall survival (OS), quality of life (QOL), and treatment-related morbidity. The pivotal trial had numerous methodologic limitations and failed to demonstrate an improvement in OS or disease response. There were some differences reported in QOL, but these data were limited by a low response rate for QOL measures. In addition, the best standard chemotherapy protocols reported in the randomized controlled trial may not reflect current practice, given the increased use of bevacizumab and temozolomide for treatment of patients with recurrent glioblastoma. No data were available to address a comparison to other treatment modalities (eg, radiation, surgery, combination therapy). The evidence is insufficient to determine the effects of the technology on health outcomes.

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# Tumor Treating Fields Therapy

## POLICY NUMBER

A.1.01.29

## DESCRIPTION

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during the course of treatment. Tumor-treatment fields therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

### **Glioblastoma Multiforme**

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults. GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (eg, bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors. The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis at 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to 1 year, and the 5-year survival rate was around 5%.

### **Clinical Context and Therapy Purpose**

The purpose of alternating electrical field therapy, more commonly known as tumor treating fields (TTF) therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

### **Treatment of Newly Diagnosed GBM**

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bischloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these two therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival rates with temozolomide are higher in patients who have O<sup>6</sup>-

methylguanine-DNA methyltransferase (*MGMT*) gene promoter methylation (see [Analysis of MGMT Promoter Methylation in Malignant Gliomas \(https://www.bcbsms.com/medical-policy-search#/policy-detail?id=6a48bedf-61a9-4770-98a0-974038e85619\)](https://www.bcbsms.com/medical-policy-search#/policy-detail?id=6a48bedf-61a9-4770-98a0-974038e85619) medical policy).

Prognostic factors for success of therapy are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice. For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially in all patients.

### **Treatment of Recurrent GBM**

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic



medications such as the antivasculature endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (eg, lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%. There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

The questions addressed in this policy are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature for this policy.

### **Patients**

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

### **Interventions**

Tumor-treatment fields (TTF) therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields. TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. Tumor-treatment fields therapy is proposed to inhibit tumor growth by two mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase. Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune, formerly NovoTTF-100A System, is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

### **Comparators**

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

The following practices are currently being used to make decisions about recurrent GBM: medical therapy.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months.

### **Outcomes**

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

### **Timing**

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.



**Setting**

The setting is outpatient care by an oncologist or neuro-oncologist.

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of tumor-treatment fields) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process. The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM [glioblastoma multiforme], following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment, and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved Novocure's request to change its products name from NovoTTF-110A System to Optune®.

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM. The device was granted priority review status in May 2015 because there was no legally marketed alternative device currently available for the treatment of newly diagnosed GBM that represents a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

## POLICY

Tumor treating fields therapy to treat glioblastoma multiforme is considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

- Adult patients ≥18 years of age
- Supratentorial tumor
- Karnofsky Performance Status score ≥70%
- Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (see Policy Guidelines).

Tumor treating fields therapy is considered **investigational** in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (eg, bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
- For brain metastases
- For cancer in areas other than the brain.

## POLICY EXCEPTIONS

Federal Employee Program (FEP) may dictate that all FDA-approved devices, drugs or biologics may not be considered investigational and thus these devices may be assessed only on the basis of their medical necessity.

## POLICY GUIDELINES

The coverage guidelines outlined in the Medical Policy Manual should not be used in lieu of the Member's specific benefit plan language.



Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth >25% compared with the smallest tumor area measured in the patient during the trial or appearance of one or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).

The Food and Drug Administration label includes the following notices:

- Patients should use Optune for at least 18 hours a day to get the best response to treatment
- Patients should finish at least 4 full weeks of therapy to get the best response to treatment. Stopping treatment before 4 weeks lowers the chances of a response to treatment.

Investigative is defined as the use of any treatment procedure, facility, equipment, drug, device, or supply not yet recognized as a generally accepted standard of good medical practice for the treatment of the condition being treated and; therefore, is not considered medically necessary. For the definition of Investigative, "generally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, and physician specialty society recommendations, and the views of medical practitioners practicing in relevant clinical areas and any other relevant factors. In order for equipment, devices, drugs or supplies [i.e, technologies], to be considered not investigative, the technology must have final approval from the appropriate governmental bodies, and scientific evidence must permit conclusions concerning the effect of the technology on health outcomes, and the technology must improve the net health outcome, and the technology must be as beneficial as any established alternative and the improvement must be attainable outside the testing/investigational setting.

## POLICY HISTORY

04/01/2014: Approved by Medical Policy Advisory Committee.

09/30/2014: Policy reviewed; no changes.

07/23/2015: Code Reference section updated for ICD-10.

11/03/2015: Policy description updated regarding devices. Policy statement unchanged. Investigative definition updated in policy guidelines section.

01/06/2016: Code Reference section updated to add HCPCS codes A4555 and E0766 with an effective date of 01/01/2016.

05/31/2016: Policy number A.1.01.29 added.

09/22/2016: Policy description updated to add section headings. Policy statement revised for clarity; intent unchanged.

08/04/2017: Policy description updated regarding treatment for patients with glioblastoma multiforme and devices. Policy statement updated to state that tumor-treatment fields therapy to treat glioblastoma multiforme (GBM) is investigational as an alternative to standard chemotherapy for patients with progressive or recurrent GBM after initial or repeat treatment with surgery, radiotherapy, and/or chemotherapy and as an adjunct to standard maintenance therapy in patients with newly diagnosed GBM following initial treatment with surgery, radiotherapy, and/or chemotherapy.

09/15/2018: Policy title changed from "Tumor-Treatment Fields Therapy for Glioblastoma" to "Tumor Treating Fields Therapy." Policy description updated regarding treatment of newly diagnosed glioblastoma multiforme (GBM) and recurrent GBM. Added the following policy statement: Tumor treating fields therapy to treat glioblastoma multiforme is considered medically necessary as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under certain conditions. Investigational statement updated to state that tumor treating fields therapy is considered investigational in all other conditions. Policy Guidelines updated to define progression. Code Reference section updated to change codes from investigational to medically necessary and add ICD-10 diagnosis codes C71.0 - C71.9.

## SOURCE(S)



## CODE REFERENCE

This may not be a comprehensive list of procedure codes applicable to this policy.

The code(s) listed below are **ONLY** medically necessary if the procedure is performed according to the "Policy" section of this document.

### Medically Necessary Codes

Code Number	Description
<b>CPT-4</b>	
<b>HCPCS</b>	
A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
A9900	Miscellaneous DME supply, accessory, and/or service component of another HCPCS code
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type
E1399	Durable medical equipment, miscellaneous
<b>ICD-10 Procedure</b>	
<b>ICD-10 Diagnosis</b>	
C71.0 - C71.9	Malignant neoplasm of brain

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# Tumor Treating Fields Therapy

## POLICY NUMBER

A.1.01.29

## DESCRIPTION

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during the course of treatment. Tumor-treatment fields therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

### **Glioblastoma Multiforme**

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults. GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (eg, bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors. The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis at 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to 1 year, and the 5-year survival rate was around 5%.

### **Clinical Context and Therapy Purpose**

The purpose of alternating electrical field therapy, more commonly known as tumor treating fields (TTF) therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

### **Treatment of Newly Diagnosed GBM**

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bischloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these two therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival rates with temozolomide are higher in patients who have O<sup>6</sup>-methylguanine-DNA methyltransferase (*MGMT*) gene promoter methylation (see [Analysis of MGMT Promoter Methylation in Malignant Gliomas \(https://www.bcbsms.com/medical-policy-search#/policy-detail?id=6a48bedf-61a9-4770-98a0-974038e85619\)](https://www.bcbsms.com/medical-policy-search#/policy-detail?id=6a48bedf-61a9-4770-98a0-974038e85619) medical policy).

Prognostic factors for success of therapy are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice. For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially in all patients.

### **Treatment of Recurrent GBM**

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment



for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (eg, lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%. There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

The questions addressed in this policy are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature for this policy.

### **Patients**

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

### **Interventions**

Tumor-treatment fields (TTF) therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields. TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. Tumor-treatment fields therapy is proposed to inhibit tumor growth by two mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase. Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune, formerly NovoTTF-100A System, is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

### **Comparators**

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

The following practices are currently being used to make decisions about recurrent GBM: medical therapy.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months.

### **Outcomes**

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

### **Timing**

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.



**Setting**

The setting is outpatient care by an oncologist or neuro-oncologist.

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of tumor-treatment fields) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process. The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM [glioblastoma multiforme], following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment, and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved Novocure's request to change its products name from NovoTTF-110A System to Optune®.

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM. The device was granted priority review status in May 2015 because there was no legally marketed alternative device currently available for the treatment of newly diagnosed GBM that represents a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

## POLICY

Tumor treating fields therapy to treat glioblastoma multiforme is considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

- Adult patients ≥18 years of age
- Supratentorial tumor
- Karnofsky Performance Status score ≥70%
- Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (see Policy Guidelines).

Tumor treating fields therapy is considered **investigational** in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (eg, bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
- For brain metastases
- For cancer in areas other than the brain.

## POLICY EXCEPTIONS

Federal Employee Program (FEP) may dictate that all FDA-approved devices, drugs or biologics may not be considered investigational and thus these devices may be assessed only on the basis of their medical necessity.

## POLICY GUIDELINES



The coverage guidelines outlined in the Medical Policy Manual should not be used in lieu of the Member's specific benefit plan language.

Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth >25% compared with the smallest tumor area measured in the patient during the trial or appearance of one or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).

The Food and Drug Administration label includes the following notices:

- Patients should use Optune for at least 18 hours a day to get the best response to treatment
- Patients should finish at least 4 full weeks of therapy to get the best response to treatment. Stopping treatment before 4 weeks lowers the chances of a response to treatment.

Investigative is defined as the use of any treatment procedure, facility, equipment, drug, device, or supply not yet recognized as a generally accepted standard of good medical practice for the treatment of the condition being treated and; therefore, is not considered medically necessary. For the definition of Investigative, "generally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, and physician specialty society recommendations, and the views of medical practitioners practicing in relevant clinical areas and any other relevant factors. In order for equipment, devices, drugs or supplies [i.e, technologies], to be considered not investigative, the technology must have final approval from the appropriate governmental bodies, and scientific evidence must permit conclusions concerning the effect of the technology on health outcomes, and the technology must improve the net health outcome, and the technology must be as beneficial as any established alternative and the improvement must be attainable outside the testing/investigational setting.

## POLICY HISTORY

04/01/2014: Approved by Medical Policy Advisory Committee.

09/30/2014: Policy reviewed; no changes.

07/23/2015: Code Reference section updated for ICD-10.

11/03/2015: Policy description updated regarding devices. Policy statement unchanged. Investigative definition updated in policy guidelines section.

01/06/2016: Code Reference section updated to add HCPCS codes A4555 and E0766 with an effective date of 01/01/2016.

05/31/2016: Policy number A.1.01.29 added.

09/22/2016: Policy description updated to add section headings. Policy statement revised for clarity; intent unchanged.

08/04/2017: Policy description updated regarding treatment for patients with glioblastoma multiforme and devices. Policy statement updated to state that tumor-treatment fields therapy to treat glioblastoma multiforme (GBM) is investigational as an alternative to standard chemotherapy for patients with progressive or recurrent GBM after initial or repeat treatment with surgery, radiotherapy, and/or chemotherapy and as an adjunct to standard maintenance therapy in patients with newly diagnosed GBM following initial treatment with surgery, radiotherapy, and/or chemotherapy.

09/15/2018: Policy title changed from "Tumor-Treatment Fields Therapy for Glioblastoma" to "Tumor Treating Fields Therapy." Policy description updated regarding treatment of newly diagnosed glioblastoma multiforme (GBM) and recurrent GBM. Added the following policy statement: Tumor treating fields therapy to treat glioblastoma multiforme is considered medically necessary as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under certain conditions. Investigational statement updated to state that tumor treating fields therapy is considered investigational in all other conditions. Policy Guidelines updated to define progression. Code Reference section updated to change codes from investigational to medically necessary and add ICD-10 diagnosis codes C71.0 - C71.9.



## SOURCE(S)

Blue Cross and Blue Shield Association Policy #1.01.29

## CODE REFERENCE

**This may not be a comprehensive list of procedure codes applicable to this policy.**

**The code(s) listed below are ONLY medically necessary if the procedure is performed according to the "Policy" section of this document.**

### Medically Necessary Codes

Code Number	Description
<b>CPT-4</b>	
<b>HCPCS</b>	
A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
A9900	Miscellaneous DME supply, accessory, and/or service component of another HCPCS code
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type
E1399	Durable medical equipment, miscellaneous
<b>ICD-10 Procedure</b>	
<b>ICD-10 Diagnosis</b>	
C71.0 - C71.9	Malignant neoplasm of brain

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Kansas City

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# Tumor-Treatment Fields Therapy

**Policy Number:** 1.01.29

**Last Review:** 9/2018

**Origination:** 12/2013

**Next Review:** 12/2018

## **Policy**

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Tumor Treating Fields Therapy when it is determined to be medically necessary because the criteria shown below are met.

Please note that this is a type of electrical stimulation that is considered a benefit exclusion in many health plan contracts.

## **When Policy Topic is covered**

Tumor treating fields therapy to treat glioblastoma multiforme is considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

- Adult patients  $\geq 18$  years of age
- Supratentorial tumor
- Karnofsky Performance Status score  $\geq 70\%$
- Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (Considerations).

## **When Policy Topic is not covered**

Tumor treatment fields therapy to treat glioblastoma is considered **investigational**, including but not limited to the following situations:

- As an adjunct to standard medical therapy (eg, bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
- For brain metastases
- For cancer in areas other than the brain.

## **Considerations**

Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth  $>25\%$  compared with the smallest tumor



area measured in the patient during the trial or appearance of 1 or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).

The Food and Drug Administration label includes the following notices:

- Patients should use Optune for at least 18 hours a day to get the best response to treatment
- Patients should finish at least 4 full weeks of therapy to get the best response to treatment. Stopping treatment before 4 weeks lowers the chances of a response to treatment.

There are no specific codes for the initial application of this system or instruction on use. The patient reapplies the transducer arrays at home after the initial instruction.

There are HCPCS codes for the system and the transducer arrays:

E0766 Electrical stimulation device, used for cancer treatment, includes all accessories, any type

A4555 Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only.

## Description of Procedure or Service

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>• With newly diagnosed glioblastoma multiforme on maintenance therapy after initial treatment</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Tumor treating fields therapy as an adjunct to standard maintenance therapy</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Standard maintenance therapy alone</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Disease-specific survival</li> <li>• Quality of life</li> <li>• Treatment-related morbidity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• With progressive or recurrent glioblastoma multiforme</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Tumor treating fields therapy as an adjunct or alternative to medical therapy</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Standard medical therapy</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Disease-specific survival</li> <li>• Quality of life</li> <li>• Treatment-related morbidity</li> </ul>

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes a randomized controlled trial (RCT). Relevant



outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

## **Background**

### **Glioblastoma Multiforme**

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.<sup>1</sup> GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (eg, bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors.<sup>1</sup> The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to 1 year, and the 5-year survival rate was around 5%.<sup>2</sup>

### **Clinical Context and Therapy Purpose**

The purpose of alternating electrical field therapy, more commonly known as tumor treating fields (TTF) therapy, is to provide a treatment option that is better



than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM

### ***Treatment of Newly Diagnosed GBM***

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these 2 therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival rates with temozolomide are higher in patients who have O<sup>6</sup>-methylguanine-DNA methyltransferase (*MGMT*) gene promoter methylation (see separate policy).

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice (see the Supplemental Information section).<sup>3</sup> For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially all patients.

### ***Treatment of Recurrent GBM***

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivasular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (eg, lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%.<sup>4</sup> There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.



The questions addressed in this evidence review are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

### ***Patients***

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

### ***Interventions***

TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields.<sup>4-6</sup> TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. TTF therapy is proposed to inhibit tumor growth by 2 mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase.<sup>5,6</sup> Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune (formerly NovoTTF-100A System) is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

### ***Comparators***

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

The following practices are currently being used to make decisions about recurrent GBM: medical therapy.



TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months.<sup>4</sup>

### **Outcomes**

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

### **Timing**

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

### **Setting**

The setting is outpatient care by an oncologist or neuro-oncologist.

### **Regulatory Status**

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.<sup>7</sup> The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved Novocure's request for a product name change from NovoTTF-110A System to Optune®.<sup>8</sup>

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.<sup>9</sup> The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."



## **Rationale**

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This evidence review was created in August 2013 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through April 5, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

For this review, 3 indications are evaluated: (1) tumor treating fields (TTF) as an adjunct to maintenance chemotherapy in newly diagnosed patients following initial treatment with surgery, radiotherapy and chemotherapy and (2) TTF as an adjunct or (3) alternative to medical therapy (eg, bevacizumab, chemotherapy) in progressive or recurrent glioblastoma multiforme (GBM).

### **Study Selection**

The PICOTS was used to select relevant studies.

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Within each category of study design, studies with larger sample size studies and longer duration were sought.

### **TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM**



## Randomized Controlled Trials

Stupp et al (2017) published results of the EF-14 multicenter, open-label phase 3 RCT that evaluated maintenance therapy with TTF for newly diagnosed GBM.<sup>10</sup> The trial included 695 patients from 83 sites who had supratentorial GBM and had completed standard treatment consisting of biopsy or surgical resection followed by radiotherapy and chemotherapy (see Table 1). A Karnofsky Performance Status (KPS) score of 70 or higher was an additional inclusion criterion to ensure independence in activities of daily living, and patients with rapidly progressing GBM following radiochemotherapy were excluded from the trial. Patients were randomized in a 2:1 fashion to TTF plus maintenance temozolomide or maintenance temozolomide alone.

All patients were seen monthly for follow-up. Quality of life (QOL) was assessed every 3 months, and magnetic resonance imaging (MRI) was performed every 2 months until tumor progression. Tumor progression on MRI was adjudicated by a central review committee blinded to treatment group. The primary outcome was progression-free survival (PFS), and the secondary outcome was overall survival (OS). The analysis was by intention-to-treat, including 26 patients from the control arm who crossed over to TTF following the planned interim analysis.

In 2014, an independent data and safety monitoring board concluded from the planned interim analysis that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended trial termination. The Food and Drug Administration approved the trial termination, and the trial was closed to recruitment with 695 of the planned 700 participants randomized. Control arm participants were allowed to cross over to the experimental treatment at this time. The interim analysis, which the Food and Drug Administration considered for the 2015 expanded approval of Optune, was published by Stupp et al (2015).<sup>11</sup> At the time of the interim analysis, data were available for 210 patients randomized to TTF plus temozolomide and 105 patients to temozolomide alone. Follow-up of the remainder of the 695 enrolled patients continued after enrollment was closed.

**Table 1. Key Randomized Controlled Trial Characteristics for Newly Diagnosed Glioblastoma**

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
<b>Stupp et al (2017)<sup>10</sup>; EF-14</b>	U.S., E.U., South Korea, Israel	83	2009-2016	<ul style="list-style-type: none"> <li>695 newly diagnosed with GBM and treated by radiochemotherapy</li> <li>KPS score <math>\geq 70</math></li> </ul>	TTF >18 h/d plus maintenance temozolomide (n=466)	Maintenance temozolomide alone (5 d every 28 d for 6 cycles) (n=229)

GBM: glioblastoma multiforme; h/d; hours per day; KPS: Karnofsky Performance Status; TTF: tumor treatment fields.

Results of the final analysis of the EF-14 trial were similar to the interim analysis and are shown in Table 2. Both PFS and OS improved with the addition of TTF therapy to standard maintenance chemotherapy (ie, temozolomide). PFS increased



by 2.7 mo ( $p < 0.001$ ) and OS increased by 4.9 mo ( $p < 0.001$ ) in the TTF group. The time to a decrease in mental function was 2.5 months longer with TTF therapy ( $p < 0.01$ ).

There was a similar percentage of dropouts at the final analysis—with 49 (11%) patients in the TTF group and 27 (12%) patients in the temozolomide alone group. More treatment cycles with temozolomide were administered in the TTF group (median, 6 for TTF group vs 5 for controls), a finding that is consistent with the longer PFS. Rates of adverse events were similar between the groups, including rates of seizures. In secondary analysis of patients who had not progressed, there was no reduction in health-related quality of life with TTF compared with temozolomide alone aside from “itchy skin”.<sup>12</sup> Interpretation of this result is limited by the low percentage of patients who completed the health-related quality of life assessments at follow-up (65.8% of the 655 patients alive at 3 months and 41.7% of the 473 patients alive at 12 months). A mixed-model analysis, which accounts for missing data, confirmed the results of the mean change from baseline analysis.

**Table 2. Key Randomized Controlled Trial Results for Newly Diagnosed Glioblastoma**

Study	Final N (%)	Median PFS (95% CI), mo	Median OS (95% CI), mo	Systemic Adverse Events, n (%)	Seizures, n (%)	Time to 6-Point Decline in MMSE Score (95% CI), mo
<b>Stupp et al (2017)<sup>10</sup></b>						
<b>TTF + temozolomide</b>	417 (89)	6.7 (6.1 to 8.1)	20.9 (19.3 to 22.7)	218 (48)	26 (6)	16.7 (14.7 to 19.0)
<b>Temozolomide alone</b>	202 (88)	4.0 (3.8 to 4.4)	16.0 (14.0 to 18.4)	94 (44)	13 (6)	14.2 (12.7 to 17.0)
<b>HR (95% CI)</b>		0.63 (0.52 to 0.76)	0.63 (0.53 to 0.76)			0.79 (0.66 to 0.95)
<b>P value</b>		<0.001	<0.001	0.58		0.01

CI: confidence interval; HR: hazard ratio; MMSE: Mini-Mental State Examination; OS: overall survival; PFS: progression-free survival; TTF: tumor treatment fields.

Tables 3 and 4 display notable gaps identified in this trial, the major limitation is the lack of patient blinding to treatment assignment. However, PFS was assessed by investigators who were blinded to treatment and placebo effects on OS were expected to be minimal. Investigators considered it practically unfeasible (due to the heat and current of the TTF therapy) and ethically unacceptable to submit the control patients to repeated shaving of the head and continuous wear of a sham device over many months.

**Table 3. Relevance Gaps**

Study; Trial	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
<b>Stupp et al (2017)<sup>10</sup>; EF-</b>			3. Possible differences in		



14

post-progression  
treatment  
affecting overall  
survival

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 4. Study Design and Conduct Gaps**

Study; Trial	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
Stupp et al (2017) <sup>10</sup> ; EF-14		1. No sham control and not blinded to treatment assignment				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

### Section Summary: TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM

The final analysis of the EF-14 trial, which included 695 patients from 83 sites, found a statistically and clinically significant increase of 2.7 months in PFS and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. There was no sham control, and patients were not blinded to treatment assignment, but PFS was assessed by blinded evaluators, and placebo effects on the objective measure of OS were likely to be minimal. There was no evidence of a negative impact of TTF therapy on health-related quality of life, except for itchy skin from the transducers.



## TTF Therapy as an Adjunct or Alternative to Medical Therapy for Progressive or Recurrent GBM

### Randomized Controlled Trials

The 2011 Food and Drug Administration approval of the NovoTTF-100A System (now called Optune) was based on a phase 3 multinational RCT (EF-11), results of which were published by Stupp et al (2012).<sup>4</sup> This trial compared TTF therapy alone with physician's choice medical therapy in 237 adults who had relapsed or progressive glioblastoma (see Table 5). Patients had failed conventional treatment with radiotherapy, chemotherapy, and/or surgery, and more than 80% of participants had failed 2 or more prior chemotherapy regimens. In this trial, the term chemotherapy also applied to targeted agents such as bevacizumab. Patient characteristics and performance of additional post-recurrence debulking surgery were similar in the 2 groups.

**Table 5. Summary of Key Randomized Controlled Trial Characteristics for Progressive or Recurrent Glioblastoma**

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
<b>Stupp et al (2012)<sup>4</sup>; EF-11</b>	U.S., E.U., Israel	28	1987-2013	<ul style="list-style-type: none"> <li>237 adults with relapsed or progressive supratentorial glioblastoma</li> <li>KPS score <math>\geq 70\%</math></li> </ul>	120 patients treated with TTF alone, 93 (78%) completed 1 cycle	117 patients treated with physician's choice of medical therapy <sup>a</sup>

EU: European Union; KPS: Karnofsky Performance Status; TTF: tumor treating fields.

<sup>a</sup> Medical therapy included bevacizumab, irinotecan, nitrosoureas, platinum-based chemotherapy (ie, carboplatin); temozolomide; or a combination of procarbazine, chloroethyl ether, and vincristine.

Participants were followed monthly, including laboratory tests. MRI images were evaluated at 2, 4, and 6 months from initiation of treatment, with subsequent MRIs performed according to local practice until disease progression. QOL questionnaires were completed every 3 months. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess mortality rates. The primary end point was OS. Secondary end points included PFS, the percentage of patients with PFS at 6 months, time to progression, 1-year survival rate, QOL, and radiologic response. All end points were evaluated using intention-to-treat analysis.

The trial did not reach its primary end point of improved survival compared with active medical therapy (see Table 6). With a median follow-up of 39 months, 93% of patients had died. There was not a statistically significant difference in survival rates at 1, 2, and 3 years between groups. Patients in the TTF group did not, however, suffer the typical systemic side effects of chemotherapy. The most common adverse event in the TTF group was grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids and did not require treatment breaks. Control participants experienced grade 2, 3, or 4 events by organ system



related to the pharmacologic activity of chemotherapy agents used. Hematologic events of grade 2 or greater were observed in 17% of chemotherapy patients compared with 3% of TTF patients. Gastrointestinal disorders of grade 2 or greater were identified in 17% of chemotherapy patients compared with 4% of TTF patients. Severe (grades 3-4) hematologic and gastrointestinal toxicity was observed in 7% of chemotherapy controls compared with 1% of the TTF group.

Longitudinal QOL data, available in 63 (27%) participants, showed no meaningful differences between groups for the domains of global health and social functioning. However, cognitive and emotional functioning domains favored TTF therapy. Symptom scale analysis was by treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.

The trial had a number of limitations (see Tables 7 and 8), that included lack of blinding and high loss to follow-up. Discontinuation of TTF therapy occurred in 22% of patients due to noncompliance or inability to handle the device, usually within the first few days. In the control group, 21 (18%) patients did not return to the treatment site, and details on disease progression and toxicity were not available. Longitudinal QOL could be analyzed only for 27% of patients who remained on study therapy for 3 months. The trial was designed as a superiority trial and did not provide adequate evidence of noninferiority.

**Table 6. Summary of Key Randomized Controlled Trial Results for Recurrent or Progressive Glioblastoma**

Study; Trial	LTFU, n (%)	Median OS, mo	Progression-Free Survival		Overall Survival (95% CI), %		
			Median, mo	Rate at 6 Months (95% CI), %	1 Year	2 Years	3 Years
Stupp et al (2012) <sup>4</sup> ; EF-11							
TTF	23 (22)	6.6	2.2	21.4 (13.5 to 29.3)	20	8 (4 to 13)	4 (1 to 8)
PCC	12 (18)	6.0	2.1	15.1 (7.8 to 22.3)	20	5 (3 to 10)	1 (0 to 3)
HR (95% CI)		0.86 (0.66 to 1.12)	0.81 (0.60 to 1.09)				
P value		0.27	0.16	0.13			

CI: confidence interval; HR: hazard ratio; LTFU: loss to follow-up; PCC: physician's choice chemotherapy; TTF: tumor treating fields.

**Table 7. Relevance Gaps**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
<b>Stupp et al (2012)<sup>4</sup>; EF-11</b>			2. Physician's choice chemotherapy		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.



<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 8. Study Design and Conduct Gaps**

Study; Trial	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>d</sup>	Data Completeness <sup>e</sup>	Power <sup>d</sup>	Statistical <sup>f</sup>
Stupp et al (2012) <sup>4</sup> ; EF-11		1. Not blinded to treatment assignment		1. 78% of TTF group completed only 1 cycle of therapy, 18% of control group lost to follow-up 1. Longitudinal QOL data were available for 27% of patients		1. Not designed as a noninferiority trial

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

QOL: quality of life.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

## Nonrandomized Comparative Studies

Kesari et al (2017) conducted a post hoc analysis of the EF-14 trial (see Stupp et al [2017] above) to evaluate the efficacy of TTF in patients who had the first recurrence.<sup>13</sup> Some patients in the temozolomide alone group crossed over to receive TTF plus chemotherapy after the first recurrence, resulting in 144 patients who received TTF fields plus chemotherapy and 60 patients who received chemotherapy alone for recurrent GBM (see Table 9). Patient characteristics and second-line treatments were well-balanced between the groups, with bevacizumab the most common second-line therapy. The median OS in patients treated with systemic therapy alone was 9.2 months (see Table 10). In comparison, the group



of patients who received TTF therapy in addition to systemic therapy had a median OS of 11.8 months ( $p=0.043$ ).

A registry study published Mrugala et al (2014) assessed OS data from patients who received NovoTTF therapy in a real-world, clinical practice setting (see Table 9).<sup>14</sup> Concurrent treatment was not captured in the registry, and it is possible that some patients received combination therapy. Median OS in the PRiDe clinical practice dataset (9.6 mo) was reported as superior to that attained in the EF-11 pivotal trial (6.6 mo,  $p<0.001$ ) (see Table 10). More patients in the PRiDe registry were treated for first recurrence (33% vs 9%), and more had received bevacizumab as prior therapy (55% vs 19%). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

**Table 9. Characteristics of Key Nonrandomized Trial Results**

Study	Study Type	Country	Dates	Participants	TTF	Controls	FU
<b>Kesari et al (2017)</b> <sup>13</sup>	EF-14 post hoc analysis	U.S., E.U., South Korea, Israel	2009-2016	204 patients with first recurrence in the EF-14 trial	144 patients treated with TTF plus second-line chemotherapy	60 patients treated with second-line chemotherapy	12.6 mo
<b>Mrugala et al (2014)</b> <sup>14</sup>	Registry	U.S. (91 centers)	2011-2013	457 patients with recurrent GBM	Patient Registry Dataset (PRiDe)	EF-11	

FU: follow-up; GBM: glioblastoma; TTF: tumor treating fields.

**Table 10. Summary of Key Nonrandomized Trial Results**

Study	Median OS, mo	Median OS With Bevacizumab, mo	
<b>Kesari et al (2017)<sup>13</sup>; EF-14</b>			
<b>TTF plus chemotherapy</b>	11.8	11.8	
<b>Chemotherapy alone</b>	9.2	9.0	
<b>Hazard ratio (95% CI)</b>	0.70 (0.48 to 1.00)	0.61 (0.37 to 0.99)	
<b>P value</b>	0.049	0.043	
		<b>1-Year OS, %</b>	<b>2-Year OS, %</b>
<b>Mrugala et al (2014)<sup>14</sup></b>			
<b>PRiDe Registry</b>	9.6	44	30
<b>EF-11</b>	6.6	20	9
<b>Hazard ratio (95% CI)</b>	0.66 (0.05 to 0.86)		
<b>P value</b>	<0.001		

CI: confidence interval; OS: overall survival, TTF: tumor treating fields.

Post hoc analyses of the EF-11 pivotal trial have been reported. Wong et al (2014) published a subgroup analysis to determine characteristics of responders and nonresponders in the active treatment and active treatment control.<sup>15</sup> They found



that responders had a lower grade of histology and lower daily dexamethasone use than nonresponders. A second post hoc analysis by Kanner et al (2014) of the EF-11 pivotal trial data was performed to evaluate OS among patients who finished at least 1 complete course of TTF or chemotherapy.<sup>16</sup> The investigators reported that median OS was 7.7 months in the TTF group compared with 5.9 months in the chemotherapy group ( $p=0.009$ ). These post hoc analyses are considered to be hypothesis-generating.

### **Section Summary: TTF Therapy as an Adjunct or Alternative to Chemotherapy for Progressive or Recurrent GBM**

The single RCT for TTF as an alternative to chemotherapy reported that outcomes following TTF therapy were similar to outcomes following standard chemotherapy. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. The noninferiority of TTF compared with chemotherapy might be considered a sufficient health benefit, if TTF reduced treatment toxicity. However, because the trial was not designed as a noninferiority trial no inferences of noninferiority compared with chemotherapy can be made. Physician's choice therapy during the trial was heterogenous, although analysis indicated that survival was not affected by choice of chemotherapy. More patients in the TTF group than in the control group did not complete the treatment course. The number of patients who contributed QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators might have been subject to bias due to the lack of blinding.

A nonrandomized post hoc evaluation of the EF-14 trial suggests that TTF may improve survival when combined with chemotherapy for recurrent GBM. This analysis should be considered hypothesis-generating, and further study in high-quality RCTs is needed.

### **Summary of Evidence**

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes an RCT. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall



survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

## **Supplemental Information**

### **Clinical Input From Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 3 physician specialty societies (one of which provided 6 responses and 2 of which provided 1 response each) and 1 academic medical center (total of 9 individual responses) while this policy was under review in 2016. There was majority support, but not consensus, for the use of tumor treatment fields therapy as an adjunct to maintenance treatment following initial therapy for glioblastoma multiforme. There was mixed support for the use of tumor treatment fields as an alternative to chemotherapy in advanced or recurrent glioblastoma multiforme.

### **Practice Guidelines and Position Statements**

National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2018) include recommendations for the treatment of glioblastoma (see Table 11).<sup>3</sup> For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate O<sup>6</sup>-methylguanine-DNA methyltransferase promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric field therapy is a category 1 recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a category 2B recommendation.



**Table 11. Guidelines for Adjuvant Treatment of Glioblastoma, by Age and Performance Status**

Age, y	KPS Score,%	Treatment Options	Category
≤70	≥60	<ul style="list-style-type: none"> <li>Standard RT plus concurrent and adjuvant temozolomide plus TTF</li> <li>Standard RT plus concurrent and adjuvant temozolomide</li> </ul>	1
≤70	<60	<ul style="list-style-type: none"> <li>Hypofractionated RT with/without concurrent or adjuvant temozolomide</li> <li>Temozolomide</li> <li>Palliative/best supportive care</li> </ul>	2A
>70	≥60	<ul style="list-style-type: none"> <li>Hypofractionated RT plus concurrent and adjuvant temozolomide</li> <li>Standard RT plus concurrent and adjuvant temozolomide plus TTF</li> <li>Temozolomide alone</li> <li>Hypofractionated brain RT alone</li> </ul>	1
>70	<60	<ul style="list-style-type: none"> <li>Hypofractionated brain RT alone</li> <li>Temozolomide alone</li> <li>Palliative/best supportive care</li> </ul>	2A

KPS: Karnofsky Performance Status; RT: radiotherapy; TTF: tumor treating fields.

### U.S. Preventive Services Task Force Recommendations

Not applicable.

### Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

### Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 12. Of particular note are the phase 3 trials evaluating TTF therapy in non-small-cell lung cancer and pancreatic cancer. TTF therapy is an active area of research for mechanisms underlying its effects on cancer cells.

**Table 12. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
<b>NCT01971281<sup>a</sup></b>	A Phase II Study of TTFields (150 kHz) Concomitant With Gemcitabine and TTFields Concomitant With Gemcitabine Plus Nab-paclitaxel for Front-line Therapy of Advanced Pancreatic Adenocarcinoma	40	Dec 2017 (ongoing)
<b>NCT01894061<sup>a</sup></b>	A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma	40	Dec 2018
<b>NCT02663271<sup>a</sup></b>	A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFields and Pulsed Bevacizumab Treatment in Patients With Bevacizumab-refractory	18	Mar 2019



NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>NCT02831959<sup>a</sup></b>	Recurrent Glioblastoma Pivotal, Open-label, Randomized Study of Radiosurgery With or Without Tumor Treating Fields (TTFields) (150kHz) for 1-10 Brain Metastases From Non-small Cell Lung Cancer (NSCLC) (METIS)	270	Jul 2019
<b>NCT02973789<sup>a</sup></b>	LUNAR: Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields) Concurrent With Standard of Care Therapies for Treatment of Stage 4 Non-small Cell Lung Cancer (NSCLC) Following Platinum Failure	534	Dec 2021
<b>NCT02743078<sup>a</sup></b>	Phase II Trial Of Optune® Plus Bevacizumab In Bevacizumab-Refractory Recurrent Glioblastoma	85	Aug 2022
<b>NCT03377491<sup>a</sup></b>	EF-27 Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields, 150kHz) Concomitant With Gemcitabine and Nab-paclitaxel for Front-line Treatment of Locally-advanced Pancreatic Adenocarcinoma (PANOVA-3)	556	Dec 2022

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

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## **Billing Coding/Physician Documentation Information**

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- A4555** Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
- E0766** Electrical stimulation device used for cancer treatment, includes all accessories, any type

### **ICD-10 Codes**

- C71.0-** Malignant neoplasm of brain code range
- C71.9**

There are no specific codes for the initial application of this system or instruction on use. The patient reapplies the transducer arrays at home after the initial instruction.

There are HCPCS codes for the system and the transducer arrays:

E0766 Electrical stimulation device, used for cancer treatment, includes all accessories, any type

A4555 Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only.

## **Additional Policy Key Words**

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N/A

## **Policy Implementation/Update Information**

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- 12/1/13 New Policy; considered investigational.
- 12/1/14 No policy statement change
- 12/1/15 No policy statement changes.
- 12/1/16 Policy statements rewritten for clarity but tumor treating fields remains investigational for all indications.



- 12/1/17 Policy statements rewritten for clarity but tumor treating fields remains investigational for all indications.
  - 9/1/18 Title changed from "Tumor Treatment Fields Therapy for Glioblastoma" to "Tumor Treating Fields Therapy". May be considered medically necessary in conjunction with maintenance temozolomide for patients with newly diagnosed glioblastoma multiforme. Investigational for all other indications.
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**MP 1.01.529**

**Tumor -Treatment Fields Therapy for Glioblastoma**

**BCBSA Ref. Policy:** 1.01.29

**Last Review:** 06/27/2018

**Effective Date:** 06/27/2018

**Section:** Durable Medical Equipment

**Related Policies**

None

## DISCLAIMER

Our medical policies are designed for informational purposes only and are not an authorization, or an explanation of benefits, or a contract. Receipt of benefits is subject to satisfaction of all terms and conditions of the coverage. Medical technology is constantly changing, and we reserve the right to review and update our policies periodically.

## POLICY

The use of FDA approved devices to generate electric tumor treatment fields (TTF) to treat histologically confirmed supratentorial glioblastoma (known also as glioblastoma multiforme [GBM] or World Health Organization [WHO] grade IV astrocytoma) is considered **medically necessary** as adjunctive treatment when all of the following criteria below are met:

1. Initial treatment with de-bulking surgery or biopsy followed by chemoradiation with concomitant temozolomide and radiotherapy has been completed with no documented tumor progression (see Policy Guidelines); and
2. TTF is initiated within 7 weeks of chemoradiation; and
3. TTF is used in combination with temozolomide; and
4. Individual has Karnofsky Performance Status score of 60 or higher and
5. Individual or caregiver has been trained and is willing and able to apply and maintain the device at least 18 hours every day.

When the above criteria are met, treatment may be authorized for up to 6 months. For treatment to be considered **medically necessary** beyond that time, the following criteria must be met:

1. Documentation is provided of compliance with proper device use for at least 18 hours a day.
2. Disease progression is not occurring despite treatment with TTF (See Policy Guidelines).

The use of devices to generate electric tumor treatment fields (TTF) is considered **investigational** when the criteria above are not met and for all other indications.

## POLICY GUIDELINES

Coverage for TTF may be allowed for up to 6 months with a medical necessity determination, and if the patient is shown to be compliant with the regimen. Continued use after 6 months will require additional documentation to show no progression of the tumor outside the radiation treatment field, worsening of the member's condition (e.g., Karnofsky performance status of < 60), or new symptoms of progressive disease.

Tumor progression may be radiologically defined as tumor growth greater than 25% compared to the



smallest measured tumor area or the appearance of one or more new GBM lesions in the brain. It is noted that pseudo-progression can appear as tumor progression on imaging and may actually be treatment effect. If pseudo-progression is identified, it must be supported through documentation by a neuro-radiologist.

There are no specific codes for the initial application of this system and instruction on use. The patient reapplies the transducer arrays at home after the initial instruction.

Effective in 2014, there are HCPCS codes for the system and the transducer arrays:

E0766: Electrical stimulation device, used for cancer treatment, includes all accessories, any type

A4555: Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only

**Table 1. Karnofsky Performance Status Scale<sup>17</sup>**

Condition	Value (%)	Level of Functional Capacity
Able to carry on normal activity and to work; no special care needed	100%	No complaints; no evidence of disease
	90%	Able to carry on normal activity; minor signs or symptoms of disease
	80%	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70%	Cares for self; unable to carry on normal activity or to do active work
	60%	Requires occasional assistance but is able to care for most personal needs
	50%	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; diseases may be progressing rapidly	40%	Disabled; requires special care and assistance
	30%	Severely disabled; hospital admission indicated although death not imminent
	20%	Very sick; hospital admission necessary; active supportive treatment necessary
	10%	Moribund; fatal processes progressing rapidly
	0%	Dead

## BENEFIT APPLICATION

### BLUE CARD/NATIONAL ACCOUNT ISSUES

State or federal mandates (e.g., FEP) may dictate that all U.S. Food and Drug Administration-approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only on the basis of their medical necessity.



**BACKGROUND****GLIOBLASTOMA MULTIFORME**

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.<sup>1</sup> GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (eg, bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors.<sup>1</sup> The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to 1 year, and the 5-year survival rate was around 5%.<sup>2</sup>

**Clinical Context and Therapy Purpose**

The purpose of alternating electrical field therapy, more commonly known as tumor treating fields (TTF) therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM

***Treatment of Newly Diagnosed GBM***

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these 2 therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival rates with temozolomide are higher in patients who have O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation (see 2.04.113 on MGMT promoter methylation for malignant gliomas).

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice (see the Supplemental Information section).<sup>3</sup> For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially all patients.

***Treatment of Recurrent GBM***

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the



antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (eg, lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%.<sup>4</sup> There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

The questions addressed in this evidence review are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

### ***Patients***

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

### ***Interventions***

TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields.<sup>4-6</sup> TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. TTF therapy is proposed to inhibit tumor growth by 2 mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase.<sup>5,6</sup> Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune (formerly NovoTTF-100A System) is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

### ***Comparators***

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

The following practices are currently being used to make decisions about recurrent GBM: medical therapy.



TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months.<sup>4</sup>

### **Outcomes**

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

### **Timing**

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

### **Setting**

The setting is outpatient care by an oncologist or neuro-oncologist.

## **REGULATORY STATUS**

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.<sup>7</sup> The FDA-approved label reads as follows: “The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted.”

In September 2014, FDA approved Novocure’s request for a product name change from NovoTTF-110A System to Optune®.<sup>8</sup>

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.<sup>9</sup> The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: “This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.”

FDA product code: NZK.

## **RATIONALE**

This evidence review was created in August 2013 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through April 5, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are



important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

For this review, 3 indications are evaluated: (1) tumor treating fields (TTF) as an adjunct to maintenance chemotherapy in newly diagnosed patients following initial treatment with surgery, radiotherapy and chemotherapy and (2) TTF as an adjunct or (3) alternative to medical therapy (eg, bevacizumab, chemotherapy) in progressive or recurrent glioblastoma multiforme (GBM).

### ***Study Selection***

The PICOTS was used to select relevant studies.

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Within each category of study design, studies with larger sample size studies and longer duration were sought.

## **TTF THERAPY AS AN ADJUNCT TO STANDARD MAINTENANCE CARE FOR NEWLY DIAGNOSED GBM**

### **Randomized Controlled Trials**

Stupp et al (2017) published results of the EF-14 multicenter, open-label phase 3 RCT that evaluated maintenance therapy with TTF for newly diagnosed GBM.<sup>10</sup> The trial included 695 patients from 83 sites who had supratentorial GBM and had completed standard treatment consisting of biopsy or surgical resection followed by radiotherapy and chemotherapy (see Table 1). A Karnofsky Performance Status (KPS) score of 70 or higher was an additional inclusion criterion to ensure independence in activities of daily living, and patients with rapidly progressing GBM following radiochemotherapy were excluded from the trial. Patients were randomized in a 2:1 fashion to TTF plus maintenance temozolomide or maintenance temozolomide alone.

All patients were seen monthly for follow-up. Quality of life (QOL) was assessed every 3 months, and magnetic resonance imaging (MRI) was performed every 2 months until tumor progression. Tumor progression on MRI was adjudicated by a central review committee blinded to treatment group. The primary outcome was progression-free survival (PFS), and the secondary outcome was overall survival (OS). The analysis was by intention-to-treat, including 26 patients from the control arm who crossed over to TTF following the planned interim analysis.

In 2014, an independent data and safety monitoring board concluded from the planned interim analysis that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended



trial termination. The Food and Drug Administration approved the trial termination, and the trial was closed to recruitment with 695 of the planned 700 participants randomized. Control arm participants were allowed to cross over to the experimental treatment at this time. The interim analysis, which the Food and Drug Administration considered for the 2015 expanded approval of Optune, was published by Stupp et al (2015).<sup>11</sup> At the time of the interim analysis, data were available for 210 patients randomized to TTF plus temozolomide and 105 patients to temozolomide alone. Follow-up of the remainder of the 695 enrolled patients continued after enrollment was closed.

**Table 1. Key Randomized Controlled Trial Characteristics for Newly Diagnosed Glioblastoma**

Study; Trial	Countries	Site s	Dates	Participants	Interventions	
					Active	Comparator
Stupp et al (2017) <sup>10</sup> ; EF-14	U.S., E.U., South Korea, Israel	83	2009-2016	<ul style="list-style-type: none"> <li>695 newly diagnosed with GBM and treated by radiochemotherapy</li> <li>KPS score <math>\geq 70</math></li> </ul>	TTF >18 h/d plus maintenance temozolomide (n=466)	Maintenance temozolomide alone (5 d every 28 d for 6 cycles) (n=229)

GBM: glioblastoma multiforme; h/d; hours per day; KPS: Karnofsky Performance Status; TTF: tumor treatment fields.

Results of the final analysis of the EF-14 trial were similar to the interim analysis and are shown in Table 2. Both PFS and OS improved with the addition of TTF therapy to standard maintenance chemotherapy (ie, temozolomide). PFS increased by 2.7 mo ( $p < 0.001$ ) and OS increased by 4.9 mo ( $p < 0.001$ ) in the TTF group. The time to a decrease in mental function was 2.5 months longer with TTF therapy ( $p < 0.01$ ).

There was a similar percentage of dropouts at the final analysis—with 49 (11%) patients in the TTF group and 27 (12%) patients in the temozolomide alone group. More treatment cycles with temozolomide were administered in the TTF group (median, 6 for TTF group vs 5 for controls), a finding that is consistent with the longer PFS. Rates of adverse events were similar between the groups, including rates of seizures. In secondary analysis of patients who had not progressed, there was no reduction in health-related quality of life with TTF compared with temozolomide alone aside from “itchy skin”.<sup>12</sup> Interpretation of this result is limited by the low percentage of patients who completed the health-related quality of life assessments at follow-up (65.8% of the 655 patients alive at 3 months and 41.7% of the 473 patients alive at 12 months). A mixed-model analysis, which accounts for missing data, confirmed the results of the mean change from baseline analysis.

**Table 2. Key Randomized Controlled Trial Results for Newly Diagnosed Glioblastoma**

Study	Final N (%)	Median PFS (95% CI), mo	Median OS (95% CI), mo	Systemic Adverse Events, n (%)		Time to 6-Point Decline in MMSE Score (95% CI), mo
				Events, n (%)	Seizures, n (%)	
Stupp et al (2017) <sup>10</sup>						
TTF + temozolomide	417 (89)	6.7 (6.1 to 8.1)	20.9 (19.3 to 22.7)	218 (48)	26 (6)	16.7 (14.7 to 19.0)



Temozolomide alone	202 (88)	4.0 (3.8 to 4.4)	16.0 (14.0 to 18.4)	94 (44)	13 (6)	14.2 (12.7 to 17.0)
HR (95% CI)		0.63 (0.52 to 0.76)	0.63 (0.53 to 0.76)			0.79 (0.66 to 0.95)
P value		<0.001	<0.001	0.58		0.01

CI: confidence interval; HR: hazard ratio; MMSE: Mini-Mental State Examination; OS: overall survival; PFS: progression-free survival; TTF: tumor treatment fields.

Tables 3 and 4 display notable gaps identified in this trial, the major limitation is the lack of patient blinding to treatment assignment. However, PFS was assessed by investigators who were blinded to treatment and placebo effects on OS were expected to be minimal. Investigators considered it practically unfeasible (due to the heat and current of the TTF therapy) and ethically unacceptable to submit the control patients to repeated shaving of the head and continuous wear of a sham device over many months.

**Table 3. Relevance Gaps**

Study; Trial	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Stupp et al (2017) <sup>10</sup> ; EF-14			3. Possible differences in post-progression treatment affecting overall survival		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 4. Study Design and Conduct Gaps**

Study; Trial	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
Stupp et al (2017) <sup>10</sup> ; EF-14		1. No sham control and not blinded to treatment assignment				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.



<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

### Section Summary: TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM

The final analysis of the EF-14 trial, which included 695 patients from 83 sites, found a statistically and clinically significant increase of 2.7 months in PFS and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. There was no sham control, and patients were not blinded to treatment assignment, but PFS was assessed by blinded evaluators, and placebo effects on the objective measure of OS were likely to be minimal. There was no evidence of a negative impact of TTF therapy on health-related quality of life, except for itchy skin from the transducers.

### TTF THERAPY AS AN ADJUNCT OR ALTERNATIVE TO MEDICAL THERAPY FOR PROGRESSIVE OR RECURRENT GBM

#### Randomized Controlled Trials

The 2011 Food and Drug Administration approval of the NovoTTF-100A System (now called Optune) was based on a phase 3 multinational RCT (EF-11), results of which were published by Stupp et al (2012).<sup>4</sup> This trial compared TTF therapy alone with physician's choice medical therapy in 237 adults who had relapsed or progressive glioblastoma (see Table 5). Patients had failed conventional treatment with radiotherapy, chemotherapy, and/or surgery, and more than 80% of participants had failed 2 or more prior chemotherapy regimens. In this trial, the term chemotherapy also applied to targeted agents such as bevacizumab. Patient characteristics and performance of additional post-recurrence debulking surgery were similar in the 2 groups.

**Table 5. Summary of Key Randomized Controlled Trial Characteristics for Progressive or Recurrent Glioblastoma**

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Stupp et al (2012) <sup>4</sup> ; EF-11	U.S., E.U., Israel	28	1987-2013	• 237 adults with relapsed or progressive supratentorial glioblastoma	120 patients treated with TTF alone, 93 (78%) completed 1	117 patients treated with physician's choice of medical therapy <sup>a</sup>



• KPS score  $\geq 70\%$  cycle

EU: European Union; KPS: Karnofsky Performance Status; TTF: tumor treating fields.

<sup>a</sup> Medical therapy included bevacizumab, irinotecan, nitrosoureas, platinum-based chemotherapy (ie, carboplatin); temozolomide; or a combination of procarbazine, chloroethyl ether, and vincristine.

Participants were followed monthly, including laboratory tests. MRI images were evaluated at 2, 4, and 6 months from initiation of treatment, with subsequent MRIs performed according to local practice until disease progression. QOL questionnaires were completed every 3 months. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess mortality rates. The primary end point was OS. Secondary end points included PFS, the percentage of patients with PFS at 6 months, time to progression, 1-year survival rate, QOL, and radiologic response. All end points were evaluated using intention-to-treat analysis.

The trial did not reach its primary end point of improved survival compared with active medical therapy (see Table 6). With a median follow-up of 39 months, 93% of patients had died. There was not a statistically significant difference in survival rates at 1, 2, and 3 years between groups. Patients in the TTF group did not, however, suffer the typical systemic side effects of chemotherapy. The most common adverse event in the TTF group was grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids and did not require treatment breaks. Control participants experienced grade 2, 3, or 4 events by organ system related to the pharmacologic activity of chemotherapy agents used. Hematologic events of grade 2 or greater were observed in 17% of chemotherapy patients compared with 3% of TTF patients. Gastrointestinal disorders of grade 2 or greater were identified in 17% of chemotherapy patients compared with 4% of TTF patients. Severe (grades 3-4) hematologic and gastrointestinal toxicity was observed in 7% of chemotherapy controls compared with 1% of the TTF group.

Longitudinal QOL data, available in 63 (27%) participants, showed no meaningful differences between groups for the domains of global health and social functioning. However, cognitive and emotional functioning domains favored TTF therapy. Symptom scale analysis was by treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.

The trial had a number of limitations (see Tables 7 and 8), that included lack of blinding and high loss to follow-up. Discontinuation of TTF therapy occurred in 22% of patients due to noncompliance or inability to handle the device, usually within the first few days. In the control group, 21 (18%) patients did not return to the treatment site, and details on disease progression and toxicity were not available. Longitudinal QOL could be analyzed only for 27% of patients who remained on study therapy for 3 months. The trial was designed as a superiority trial and did not provide adequate evidence of noninferiority.

**Table 6. Summary of Key Randomized Controlled Trial Results for Recurrent or Progressive Glioblastoma**

Study; Trial	LTFU, n (%)	Median OS, mo	Progression-Free Survival		Overall Survival (95% CI), %		
			Median, mo	Rate at 6 Months (95% CI), %	1 Year	2 Years	3 Years
Stupp et al (2012) <sup>4</sup> ; EF-							



11							
TTF	23 (22)	6.6	2.2	21.4 (13.5 to 29.3)	20	8 (4 to 13)	4 (1 to 8)
PCC	12 (18)	6.0	2.1	15.1 (7.8 to 22.3)	20	5 (3 to 10)	1 (0 to 3)
HR (95% CI)		0.86 (0.66 to 1.12)	0.81 (0.60 to 1.09)				
P value		0.27	0.16	0.13			

CI: confidence interval; HR: hazard ratio; LTFU: loss to follow-up; PCC: physician's choice chemotherapy; TTF: tumor treating fields.

**Table 7. Relevance Gaps**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Stupp et al (2012) <sup>4</sup> ; EF-11			2. Physician's choice chemotherapy		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 8. Study Design and Conduct Gaps**

Study; Trial	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>d</sup>	Data Completeness <sup>e</sup>	Power <sup>d</sup>	Statistical <sup>f</sup>
Stupp et al (2012) <sup>4</sup> ; EF-11		1. Not blinded to treatment assignment		1. 78% of TTF group completed only 1 cycle of therapy, 18% of control group lost to follow-up 1. Longitudinal QOL data were available for 27% of patients		1. Not designed as a noninferiority trial

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

QOL: quality of life.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.



<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

### Nonrandomized Comparative Studies

Kesari et al (2017) conducted a post hoc analysis of the EF-14 trial (see Stupp et al [2017] above) to evaluate the efficacy of TTF in patients who had the first recurrence.<sup>13</sup> Some patients in the temozolomide alone group crossed over to receive TTF plus chemotherapy after the first recurrence, resulting in 144 patients who received TTF fields plus chemotherapy and 60 patients who received chemotherapy alone for recurrent GBM (see Table 9). Patient characteristics and second-line treatments were well-balanced between the groups, with bevacizumab the most common second-line therapy. The median OS in patients treated with systemic therapy alone was 9.2 months (see Table 10). In comparison, the group of patients who received TTF therapy in addition to systemic therapy had a median OS of 11.8 months (p=0.043).

A registry study published Mrugala et al (2014) assessed OS data from patients who received NovoTTF therapy in a real-world, clinical practice setting (see Table 9).<sup>14</sup> Concurrent treatment was not captured in the registry, and it is possible that some patients received combination therapy. Median OS in the PRiDe clinical practice dataset (9.6 mo) was reported as superior to that attained in the EF-11 pivotal trial (6.6 mo, p<0.001) (see Table 10). More patients in the PRiDe registry were treated for first recurrence (33% vs 9%), and more had received bevacizumab as prior therapy (55% vs 19%). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

**Table 9. Characteristics of Key Nonrandomized Trial Results**

Study	Study Type	Country	Dates	Participants	TTF	Controls	FU
Kesari et al (2017) <sup>13</sup>	EF-14 post hoc analysis	U.S., E.U., South Korea, Israel	2009-2016	204 patients with first recurrence in the EF-14 trial	144 patients treated with TTF plus second-line chemotherapy	60 patients treated with second-line chemotherapy	12.6 mo
Mrugala et al (2014) <sup>14</sup>	Registry	U.S. (91 centers)	2011-2013	457 patients with recurrent GBM	Patient Registry Dataset (PRiDe)	EF-11	

FU: follow-up; GBM: glioblastoma; TTF: tumor treating fields.

**Table 10. Summary of Key Nonrandomized Trial Results**

Study	Median OS, mo	Median OS With Bevacizumab, mo
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Kesari et al (2017) <sup>13</sup> ; EF-14			
TTF plus chemotherapy	11.8	11.8	
Chemotherapy alone	9.2	9.0	
Hazard ratio (95% CI)	0.70 (0.48 to 1.00)	0.61 (0.37 to 0.99)	
P value	0.049	0.043	
		<b>1-Year OS, %</b>	<b>2-Year OS, %</b>
Mrugala et al (2014) <sup>14</sup>			
PRiDe Registry	9.6	44	30
EF-11	6.6	20	9
Hazard ratio (95% CI)	0.66 (0.05 to 0.86)		
P value	<0.001		

CI: confidence interval; OS: overall survival, TTF: tumor treating fields.

Post hoc analyses of the EF-11 pivotal trial have been reported. Wong et al (2014) published a subgroup analysis to determine characteristics of responders and nonresponders in the active treatment and active treatment control.<sup>15</sup> They found that responders had a lower grade of histology and lower daily dexamethasone use than nonresponders. A second post hoc analysis by Kanner et al (2014) of the EF-11 pivotal trial data was performed to evaluate OS among patients who finished at least 1 complete course of TTF or chemotherapy.<sup>16</sup> The investigators reported that median OS was 7.7 months in the TTF group compared with 5.9 months in the chemotherapy group (p=0.009). These post hoc analyses are considered to be hypothesis-generating.

#### Section Summary: TTF Therapy as an Adjunct or Alternative to Chemotherapy for Progressive or Recurrent GBM

The single RCT for TTF as an alternative to chemotherapy reported that outcomes following TTF therapy were similar to outcomes following standard chemotherapy. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. The noninferiority of TTF compared with chemotherapy might be considered a sufficient health benefit, if TTF reduced treatment toxicity. However, because the trial was not designed as a noninferiority trial no inferences of noninferiority compared with chemotherapy can be made. Physician's choice therapy during the trial was heterogeneous, although analysis indicated that survival was not affected by choice of chemotherapy. More patients in the TTF group than in the control group did not complete the treatment course. The number of patients who contributed QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators might have been subject to bias due to the lack of blinding.

A nonrandomized post hoc evaluation of the EF-14 trial suggests that TTF may improve survival when combined with chemotherapy for recurrent GBM. This analysis should be considered hypothesis-generating, and further study in high-quality RCTs is needed.

#### SUMMARY OF EVIDENCE

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes an RCT. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was



assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

#### SUPPLEMENTAL INFORMATION

##### CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 3 physician specialty societies (one of which provided 6 responses and 2 of which provided 1 response each) and 1 academic medical center (total of 9 individual responses) while this policy was under review in 2016. There was majority support, but not consensus, for use of tumor treatment field's therapy as an adjunct to maintenance treatment following initial therapy for glioblastoma multiforme. There was mixed support for use of tumor treatment fields as an alternative to chemotherapy in advanced or recurrent glioblastoma multiforme.

**PRACTICE GUIDELINES AND POSITION STATEMENTS** National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2018) include recommendations for the treatment of glioblastoma (see Table 11).<sup>3</sup> For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate O<sup>6</sup>-methylguanine-DNA methyltransferase promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric field therapy is a category 1 recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a category 2B recommendation.

**Table 11. Guidelines for Adjuvant Treatment of Glioblastoma, by Age and Performance Status**

Age, y	KPS		Treatment Options	Category
	Score, %			
≤70	≥60	• Standard RT plus concurrent and adjuvant temozolomide plus TTF		1



≤70	<60	<ul style="list-style-type: none"> <li>• Standard RT plus concurrent and adjuvant temozolomide</li> <li>• Hypofractionated RT with/without concurrent or adjuvant temozolomide</li> <li>• Temozolomide</li> <li>• Palliative/best supportive care</li> </ul>	2A
>70	≥60	<ul style="list-style-type: none"> <li>• Hypofractionated RT plus concurrent and adjuvant temozolomide</li> <li>• Standard RT plus concurrent and adjuvant temozolomide plus TTF</li> <li>• Temozolomide alone</li> <li>• Hypofractionated brain RT alone</li> </ul>	1
>70	<60	<ul style="list-style-type: none"> <li>• Hypofractionated brain RT alone</li> <li>• Temozolomide alone</li> <li>• Palliative/best supportive care</li> </ul>	2A

KPS: Karnofsky Performance Status; RT: radiotherapy; TTF: tumor treating fields.

#### U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

#### MEDICARE NATIONAL COVERAGE

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

#### ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 12. Of particular note are the phase 3 trials evaluating TTF therapy in non-small-cell lung cancer and pancreatic cancer. TTF therapy is an active area of research for mechanisms underlying its effects on cancer cells.

**Table 12. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
NCT01971281 <sup>a</sup>	A Phase II Study of TTFields (150 kHz) Concomitant With Gemcitabine and TTFields Concomitant With Gemcitabine Plus Nab-paclitaxel for Front-line Therapy of Advanced Pancreatic Adenocarcinoma	40	Dec 2017 (ongoing)
NCT01894061 <sup>a</sup>	A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma	40	Dec 2018
NCT02663271 <sup>a</sup>	A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFields and Pulsed Bevacizumab Treatment in Patients With Bevacizumab-refractory Recurrent Glioblastoma	18	Mar 2019
NCT02831959 <sup>a</sup>	Pivotal, Open-label, Randomized Study of Radiosurgery With or Without Tumor Treating Fields (TTFields) (150kHz) for 1-10 Brain Metastases From Non-small Cell Lung Cancer (NSCLC) (METIS)	270	Jul 2019



NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02973789 <sup>a</sup>	LUNAR: Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields) Concurrent With Standard of Care Therapies for Treatment of Stage 4 Non-small Cell Lung Cancer (NSCLC) Following Platinum Failure	534	Dec 2021
NCT02743078 <sup>a</sup>	Phase II Trial Of Optune® Plus Bevacizumab In Bevacizumab-Refractory Recurrent Glioblastoma	85	Aug 2022
NCT03377491 <sup>a</sup>	EF-27 Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields, 150kHz) Concomitant With Gemcitabine and Nab-paclitaxel for Front-line Treatment of Locally-advanced Pancreatic Adenocarcinoma (PANOVA-3)	556	Dec 2022

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

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#### CODES

Codes	Number	Description
CPT Codes		No specific CPT code- See Policy Guidelines
	191.0-191.9	Malignant neoplasm of brain code range
HCPCS Codes	A4555	Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only
	E0766	Electrical stimulation device, used for cancer treatment, includes all accessories, any type
ICD-10-CM		Investigational for all relevant diagnoses
	C71.0-C71.9	Malignant neoplasm of brain code range
ICD-10-PCS		Not applicable. Policy is only for outpatient services. ICD-10-PCS codes are only used for inpatient services.
Type of Service		
Place of Service		

#### POLICY HISTORY

Date	Action	Description
08/14/14	Replace policy	Policy updated with literature review through June 26, 2014.



		References 8 and 16-17 added. Editorial revisions made to rationale section. Policy statement unchanged.
08/13/15	Replace policy	Policy updated with literature review through July 8, 2015; references 10-11 removed and 10-12 added. Policy statement unchanged.
08/11/16	Replace policy	Policy updated with literature review through July 18, 2016, and results of clinical vetting; reference 13 added. Policy statements rewritten for clarity but tumor treating fields remains investigational for all indications.
12/23/2016	Replace policy	Blue Cross of Idaho adopted new policy statement and policy guidelines to reflect NCCN 2A recommendations. Medically necessary indication with specific criteria.
07/25/17	Replace policy	Blue Cross of Idaho adopted changes as noted, with no change to policy statements. Policy updated with literature review through June 5, 2017; no references added. No change to policy statements or policy guidelines.
03/29/18	Update only	Medical policy renumbered from 1.01.29 to 1.01.529.
06/27/18	Replace policy	Policy updated with literature review through April 5, 2018; references 10, and 12-13, and 17 added. No change to policy statements or policy guidelines.



# Protocol

## Tumor Treating Fields Therapy

(10129)

(Formerly Tumor Treatment Fields Therapy for Glioblastoma)

Medical Benefit		Effective Date: 10/01/18	Next Review Date: 07/19
Preauthorization	Yes	Review Dates: 09/15, 05/16, 09/16, 09/17, 07/18	

### Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"><li>With newly diagnosed glioblastoma multiforme on maintenance therapy after initial treatment</li></ul>	Interventions of interest are: <ul style="list-style-type: none"><li>Tumor treating fields therapy as an adjunct to standard maintenance therapy</li></ul>	Comparators of interest are: <ul style="list-style-type: none"><li>Standard maintenance therapy alone</li></ul>	Relevant outcomes include: <ul style="list-style-type: none"><li>Overall survival</li><li>Disease-specific survival</li><li>Quality of life</li><li>Treatment-related morbidity</li></ul>
Individuals: <ul style="list-style-type: none"><li>With progressive or recurrent glioblastoma multiforme</li></ul>	Interventions of interest are: <ul style="list-style-type: none"><li>Tumor treating fields therapy as an adjunct or alternative to medical therapy</li></ul>	Comparators of interest are: <ul style="list-style-type: none"><li>Standard medical therapy</li></ul>	Relevant outcomes include: <ul style="list-style-type: none"><li>Overall survival</li><li>Disease-specific survival</li><li>Quality of life</li><li>Treatment-related morbidity</li></ul>

### DESCRIPTION

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

### SUMMARY OF EVIDENCE

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes a randomized controlled trial (RCT). Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (i.e., temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited.



The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

## POLICY

Tumor treating fields therapy to treat glioblastoma multiforme is considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

- Adult patients  $\geq 22$  years of age
- Supratentorial tumor
- Karnofsky Performance Status score  $\geq 70\%$
- Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (see Policy Guidelines).

Tumor treating fields therapy is considered **investigational** in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (e.g., bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
- For brain metastases
- For cancer in areas other than the brain.

## POLICY GUIDELINES

Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth  $> 25\%$  compared with the smallest tumor area measured in the patient during the trial or appearance of one or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).



The Food and Drug Administration label includes the following notices:

- Patients should use Optune for at least 18 hours a day to get the best response to treatment
- Patients should finish at least four full weeks of therapy to get the best response to treatment. Stopping treatment before four weeks lowers the chances of a response to treatment.

## MEDICARE ADVANTAGE

For Medicare Advantage tumor-treatment fields therapy is considered **not medically necessary**.

## BACKGROUND

### GLIOBLASTOMA MULTIFORME

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.<sup>1</sup> GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (e.g., bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors.<sup>1</sup> The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to one year, and the five-year survival rate was around 5%.<sup>2</sup>

### Clinical Context and Therapy Purpose

The purpose of alternating electrical field therapy, more commonly known as TTF therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

### Treatment of Newly Diagnosed GBM

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these two therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for five days of every 28-day cycle for six cycles. Response and overall survival rates with temozolomide are higher in patients who have O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation.

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice.<sup>3</sup> For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially all patients.



## Treatment of Recurrent GBM

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (e.g., lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at six months is less than 20%.<sup>4</sup> There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

The questions addressed in this protocol are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

### Patients

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

### Interventions

TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields.<sup>4-6</sup> TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. TTF therapy is proposed to inhibit tumor growth by two mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase.<sup>5,6</sup> Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune (formerly NovoTTF-100A System) is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma,<sup>4</sup> disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and two to three days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is one month, with the continuation of treatment available until recurrence.

### Comparators

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.



The following practices are currently being used to make decisions about recurrent GBM: medical therapy.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds three to five months.<sup>4</sup>

#### Outcomes

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

#### Timing

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

#### Setting

The setting is outpatient care by an oncologist or neuro-oncologist.

### REGULATORY STATUS

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.<sup>7</sup> The FDA-approved label reads as follows: “The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted.”

In September 2014, the FDA approved Novocure’s request for a product name change from NovoTTF-110A System to Optune®.<sup>8</sup>

In October 2015, the FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.<sup>9</sup> The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: “This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.”

FDA product code: NZK.

### RELATED PROTOCOLS

Intensity-Modulated Radiotherapy: Central Nervous System Tumors

Intracavitary Balloon Catheter Brain Brachytherapy for Malignant Gliomas



## Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

## REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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<b>1.01.29</b>	<b>Tumor Treating Fields Therapy</b>		
<b>Original Policy Date:</b>	October 31, 2014	<b>Effective Date:</b>	November 1, 2018
<b>Section:</b>	1.0 Durable Medical Equipment	<b>Page:</b>	Page 1 of 16

### Policy Statement

Tumor treating fields therapy to treat glioblastoma multiforme may be considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in patients with **newly diagnosed** glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

- Adult patients 18 years old or older
- Supratentorial tumor
- Karnofsky Performance Status score greater than or equal to 60%
- Documentation the patient understands device use, including the requirement for a shaved head, use for at least 18 hours a day for a minimum of 4 weeks, and is willing to comply with use criteria according to the Food and Drug Administration label (see Policy Guidelines section)

Tumor treating fields therapy is considered **investigational** in all other conditions, including but not limited to the following situations:

- As an adjunct or alternative to standard medical therapy for progressive or recurrent tumors (e.g., bevacizumab, chemotherapy) for patients with **progressive or recurrent** glioblastoma multiforme\* (see Policy Guidelines section)
- For brain metastases
- For cancer in areas other than the brain

### Policy Guidelines

\*Use for progressive or recurrent disease is a level 2B recommendation in NCCN guidelines (as compared to level 1 for newly diagnosed). Typically, a category 1 or 2A recommendation is followed, but not 2B. Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth greater than 25% compared with the smallest tumor area measured in the patient during the trial or appearance of 1 or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).

The Food and Drug Administration label includes the following notices:

- Patients should use Optune for at least 18 hours a day to get the best response to treatment
- Patients should finish at least 4 full weeks of therapy to get the best response to treatment. Stopping treatment before 4 weeks lowers the chances of a response to treatment

### Coding

There are no specific codes for the initial application of this system or instruction on use. The patient reapplies the transducer arrays at home after the initial instruction.

There are HCPCS codes for the system and the transducer arrays:

- **A4555:** Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
- **E0766:** Electrical stimulation device used for cancer treatment, includes all accessories, any type



## Description

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

## Related Policies

- Analysis of MGMT Promoter Methylation in Malignant Gliomas
- Intensity-Modulated Radiotherapy: Central Nervous System Tumors
- Intracavitary Balloon Catheter Brain Brachytherapy for Malignant Gliomas or Metastasis to the Brain
- Intraoperative Radiotherapy
- Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

## Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## Regulatory Status

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.<sup>7</sup> The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved Novocure's request for a product name change from NovoTTF-110A System to Optune®.<sup>8</sup>

In October 2015, the FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.<sup>9</sup> The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients



with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

FDA product code: NZK.

## Rationale

### Background

#### **Glioblastoma Multiforme**

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.<sup>1</sup> GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (e.g., bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors.<sup>1</sup> The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to 1 year, and the 5-year survival rate was around 5%.<sup>2</sup>

#### **Clinical Context and Therapy Purpose**

The purpose of alternating electrical field therapy, more commonly known as tumor treating fields (TTF) therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

#### ***Treatment of Newly Diagnosed Glioblastoma Multiforme***

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these 2 therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival rates with temozolomide are higher in patients who have O<sup>6</sup>-methylguanine-DNA methyltransferase (*MGMT*) gene promoter methylation (see Blue Shield of California Medical Policy: Analysis of *MGMT* Promoter Methylation in Malignant Gliomas on *MGMT* promotor methylation for malignant gliomas).

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice (see the Supplemental Information section).<sup>3</sup> For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially all patients.

#### ***Treatment of Recurrent Glioblastoma Multiforme***

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug



bevacizumab, alkylating agents such as nitrosoureas (e.g., lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%.<sup>4</sup> There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

The questions addressed in this evidence review are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

### ***Patients***

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

### ***Interventions***

TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields.<sup>4-6</sup> TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. TTF therapy is proposed to inhibit tumor growth by 2 mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase.<sup>5,6</sup> Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune (formerly NovoTTF-100A System) is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

### ***Comparators***

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

The following practices are currently being used to make decisions about recurrent GBM: medical therapy.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months.<sup>4</sup>



**Outcomes**

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

**Timing**

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

**Setting**

The setting is outpatient care by an oncologist or neuro-oncologist.

**Literature Review**

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

For this review, 3 indications are evaluated: (1) tumor treating fields (TTF) as an adjunct to maintenance chemotherapy in newly diagnosed patients following initial treatment with surgery, radiotherapy and chemotherapy and (2) TTF as an adjunct or (3) alternative to medical therapy (e.g., bevacizumab, chemotherapy) in progressive or recurrent glioblastoma multiforme (GBM).

**Study Selection**

The PICOTS was used to select relevant studies.

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Within each category of study design, studies with larger sample size studies and longer duration were sought.

**TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM  
Randomized Controlled Trials**

Stupp et al (2017) published results of the EF-14 multicenter, open-label phase 3 RCT that evaluated maintenance therapy with TTF for newly diagnosed GBM.<sup>10</sup> The trial included 695 patients from 83 sites who had supratentorial GBM and had completed standard treatment consisting of biopsy or surgical resection followed by radiotherapy and chemotherapy (see Table 1). A Karnofsky Performance Status (KPS) score of 70 or higher was an additional inclusion



criterion to ensure independence in activities of daily living, and patients with rapidly progressing GBM following radiochemotherapy were excluded from the trial. Patients were randomized in a 2:1 fashion to TTF plus maintenance temozolomide or maintenance temozolomide alone.

All patients were seen monthly for follow-up. Quality of life (QOL) was assessed every 3 months, and magnetic resonance imaging (MRI) was performed every 2 months until tumor progression. Tumor progression on MRI was adjudicated by a central review committee blinded to treatment group. The primary outcome was progression-free survival (PFS), and the secondary outcome was overall survival (OS). The analysis was by intention-to-treat, including 26 patients from the control arm who crossed over to TTF following the planned interim analysis.

In 2014, an independent data and safety monitoring board concluded from the planned interim analysis that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended trial termination. The Food and Drug Administration approved the trial termination, and the trial was closed to recruitment with 695 of the planned 700 participants randomized. Control arm participants were allowed to cross over to the experimental treatment at this time. The interim analysis, which the Food and Drug Administration considered for the 2015 expanded approval of Optune, was published by Stupp et al (2015).<sup>11</sup> At the time of the interim analysis, data were available for 210 patients randomized to TTF plus temozolomide and 105 patients to temozolomide alone. Follow-up of the remainder of the 695 enrolled patients continued after enrollment was closed.

**Table 1. Key Randomized Controlled Trial Characteristics for Newly Diagnosed Glioblastoma**

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Stupp et al (2017) <sup>10</sup> ; EF-14	U.S., E.U., South Korea, Israel	83	2009-2016	<ul style="list-style-type: none"> <li>695 newly diagnosed with GBM and treated by radiochemotherapy</li> <li>KPS score <math>\geq 70</math></li> </ul>	TTF >18 h/d plus maintenance temozolomide (n=466)	Maintenance temozolomide alone (5 d every 28 d for 6 cycles) (n=229)

GBM: glioblastoma multiforme; h/d; hours per day; KPS: Karnofsky Performance Status; TTF: tumor treatment fields.

Results of the final analysis of the EF-14 trial were similar to the interim analysis and are shown in Table 2. Both PFS and OS improved with the addition of TTF therapy to standard maintenance chemotherapy (i.e., temozolomide). PFS increased by 2.7 mo ( $p < 0.001$ ) and OS increased by 4.9 mo ( $p < 0.001$ ) in the TTF group. The time to a decrease in mental function was 2.5 months longer with TTF therapy ( $p < 0.01$ ).

There was a similar percentage of dropouts at the final analysis—with 49 (11%) patients in the TTF group and 27 (12%) patients in the temozolomide alone group. More treatment cycles with temozolomide were administered in the TTF group (median, 6 for TTF group vs 5 for controls), a finding that is consistent with the longer PFS. Rates of adverse events were similar between the groups, including rates of seizures. In secondary analysis of patients who had not progressed, there was no reduction in health-related quality of life with TTF compared with temozolomide alone aside from “itchy skin”.<sup>12</sup> Interpretation of this result is limited by the low percentage of patients who completed the health-related quality of life assessments at follow-up (65.8% of the 655 patients alive at 3 months and 41.7% of the 473 patients alive at 12 months). A mixed-model analysis, which accounts for missing data, confirmed the results of the mean change from baseline analysis.



**Table 2. Key Randomized Controlled Trial Results for Newly Diagnosed Glioblastoma**

Study	Final N (%)	Median PFS (95% CI), mo	Median OS (95% CI), mo	Systemic Adverse Events, n (%)	Seizures, n (%)	Time to 6-Point Decline in MMSE Score (95% CI), mo
Stupp et al (2017) <sup>10</sup>						
TTF + temozolomide	417 (89)	6.7 (6.1 to 8.1)	20.9 (19.3 to 22.7)	218 (48)	26 (6)	16.7 (14.7 to 19.0)
Temozolomide alone	202 (88)	4.0 (3.8 to 4.4)	16.0 (14.0 to 18.4)	94 (44)	13 (6)	14.2 (12.7 to 17.0)
HR (95% CI)		0.63 (0.52 to 0.76)	0.63 (0.53 to 0.76)			0.79 (0.66 to 0.95)
P value		<0.001	<0.001	0.58		0.01

CI: confidence interval; HR: hazard ratio; MMSE: Mini-Mental State Examination; OS: overall survival; PFS: progression-free survival; TTF: tumor treatment fields.

Tables 3 and 4 display notable gaps identified in this trial, the major limitation is the lack of patient blinding to treatment assignment. However, PFS was assessed by investigators who were blinded to treatment and placebo effects on OS were expected to be minimal. Investigators considered it practically unfeasible (due to the heat and current of the TTF therapy) and ethically unacceptable to submit the control patients to repeated shaving of the head and continuous wear of a sham device over many months.

**Table 3. Relevance Gaps**

Study; Trial	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Stupp et al (2017) <sup>10</sup> ; EF-14			3. Possible differences in post-progression treatment affecting overall survival		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 4. Study Design and Conduct Gaps**

Study; Trial	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
Stupp et al (2017) <sup>10</sup> ; EF-14		1. No sham control and not blinded to treatment assignment				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).



<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

### Section Summary: TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM

The final analysis of the EF-14 trial, which included 695 patients from 83 sites, found a statistically and clinically significant increase of 2.7 months in PFS and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (i.e., temozolomide) in patients with newly diagnosed GBM. There was no sham control, and patients were not blinded to treatment assignment, but PFS was assessed by blinded evaluators, and placebo effects on the objective measure of OS were likely to be minimal. There was no evidence of a negative impact of TTF therapy on health-related quality of life, except for itchy skin from the transducers.

### TTF Therapy as an Adjunct or Alternative to Medical Therapy for Progressive or Recurrent GBM Randomized Controlled Trials

The 2011 Food and Drug Administration approval of the NovoTTF-100A System (now called Optune) was based on a phase 3 multinational RCT (EF-11), results of which were published by Stupp et al (2012).<sup>4</sup> This trial compared TTF therapy alone with physician's choice medical therapy in 237 adults who had relapsed or progressive glioblastoma (see Table 5). Patients had failed conventional treatment with radiotherapy, chemotherapy, and/or surgery, and more than 80% of participants had failed 2 or more prior chemotherapy regimens. In this trial, the term chemotherapy also applied to targeted agents such as bevacizumab. Patient characteristics and performance of additional post-recurrence debulking surgery were similar in the 2 groups.

**Table 5. Summary of Key Randomized Controlled Trial Characteristics for Progressive or Recurrent Glioblastoma**

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Stupp et al (2012) <sup>4</sup> ; EF-11	U.S., E.U., Israel	28	1987-2013	<ul style="list-style-type: none"> <li>237 adults with relapsed or progressive supratentorial glioblastoma</li> <li>KPS score <math>\geq 70\%</math></li> </ul>	120 patients treated with TTF alone, 93 (78%) completed 1 cycle	117 patients treated with physician's choice of medical therapy <sup>a</sup>

EU: European Union; KPS: Karnofsky Performance Status; TTF: tumor treating fields.

<sup>a</sup> Medical therapy included bevacizumab, irinotecan, nitrosoureas, platinum-based chemotherapy (i.e., carboplatin); temozolomide; or a combination of procarbazine, chloroethyl ether, and vincristine.

Participants were followed monthly, including laboratory tests. MRI images were evaluated at 2, 4, and 6 months from initiation of treatment, with subsequent MRIs performed according to local practice until disease progression. QOL questionnaires were completed every 3 months. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess mortality rates. The primary end point was OS. Secondary end points included PFS, the percentage of patients with PFS at 6 months, time to progression, 1-year survival rate, QOL, and radiologic response. All end points were evaluated using intention-to-treat analysis.

The trial did not reach its primary end point of improved survival compared with active medical therapy (see Table 6). With a median follow-up of 39 months, 93% of patients had died. There was not a statistically significant difference in survival rates at 1, 2, and 3 years between groups. Patients in the TTF group did not, however, suffer the typical systemic side effects of chemotherapy. The most common adverse event in the TTF group was grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids and did not require treatment breaks. Control participants experienced grade 2, 3, or 4 events by organ system related to the pharmacologic activity of chemotherapy agents used. Hematologic events of



grade 2 or greater were observed in 17% of chemotherapy patients compared with 3% of TTF patients. Gastrointestinal disorders of grade 2 or greater were identified in 17% of chemotherapy patients compared with 4% of TTF patients. Severe (grades 3-4) hematologic and gastrointestinal toxicity was observed in 7% of chemotherapy controls compared with 1% of the TTF group.

Longitudinal QOL data, available in 63 (27%) participants, showed no meaningful differences between groups for the domains of global health and social functioning. However, cognitive and emotional functioning domains favored TTF therapy. Symptom scale analysis was by treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.

The trial had a number of limitations (see Tables 7 and 8), that included lack of blinding and high loss to follow-up. Discontinuation of TTF therapy occurred in 22% of patients due to noncompliance or inability to handle the device, usually within the first few days. In the control group, 21 (18%) patients did not return to the treatment site, and details on disease progression and toxicity were not available. Longitudinal QOL could be analyzed only for 27% of patients who remained on study therapy for 3 months. The trial was designed as a superiority trial and did not provide adequate evidence of noninferiority.

**Table 6. Summary of Key Randomized Controlled Trial Results for Recurrent or Progressive Glioblastoma**

Study; Trial	LTFU, n (%)	Median OS, mo	Progression-Free Survival		Overall Survival (95% CI), %		
			Median, mo	Rate at 6 Months (95% CI), %	1 Year	2 Years	3 Years
Stupp et al (2012) <sup>4</sup> ; EF-11							
TTF	23 (22)	6.6	2.2	21.4 (13.5 to 29.3)	20	8 (4 to 13)	4 (1 to 8)
PCC	12 (18)	6.0	2.1	15.1 (7.8 to 22.3)	20	5 (3 to 10)	1 (0 to 3)
HR (95% CI)		0.86 (0.66 to 1.12)	0.81 (0.60 to 1.09)				
P value		0.27	0.16	0.13			

CI: confidence interval; HR: hazard ratio; LTFU: loss to follow-up; PCC: physician's choice chemotherapy; TTF: tumor treating fields.

**Table 7. Relevance Gaps**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Stupp et al (2012) <sup>4</sup> ; EF-11			2. Physician's choice chemotherapy		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 8. Study Design and Conduct Gaps**

Study; Trial	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>d</sup>	Data Completeness <sup>e</sup>	Power <sup>d</sup>	Statistical <sup>f</sup>
Stupp et al (2012) <sup>4</sup> ; EF-11		1. Not blinded to		1. 78% of TTF group completed only 1 cycle of therapy, 18%		1. Not designed as a



Study; Trial	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>d</sup>	Data Completeness <sup>e</sup>	Power <sup>d</sup>	Statistical <sup>f</sup>
		treatment assignment		of control group lost to follow-up 1. Longitudinal QOL data were available for 27% of patients		noninferiority trial

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

QOL: quality of life.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

### Nonrandomized Comparative Studies

Kesari et al (2017) conducted a post hoc analysis of the EF-14 trial (see Stupp et al [2017] above) to evaluate the efficacy of TTF in patients who had the first recurrence.<sup>13</sup> Some patients in the temozolomide alone group crossed over to receive TTF plus chemotherapy after the first recurrence, resulting in 144 patients who received TTF fields plus chemotherapy and 60 patients who received chemotherapy alone for recurrent GBM (see Table 9). Patient characteristics and second-line treatments were well-balanced between the groups, with bevacizumab the most common second-line therapy. The median OS in patients treated with systemic therapy alone was 9.2 months (see Table 10). In comparison, the group of patients who received TTF therapy in addition to systemic therapy had a median OS of 11.8 months (p=0.043).

A registry study published Mrugala et al (2014) assessed OS data from patients who received NovoTTF therapy in a real-world, clinical practice setting (see Table 9).<sup>14</sup> Concurrent treatment was not captured in the registry, and it is possible that some patients received combination therapy. Median OS in the PRiDe clinical practice dataset (9.6 mo) was reported as superior to that attained in the EF-11 pivotal trial (6.6 mo, p<0.001) (see Table 10). More patients in the PRiDe registry were treated for first recurrence (33% vs 9%), and more had received bevacizumab as prior therapy (55% vs 19%). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

**Table 9. Characteristics of Key Nonrandomized Trial Results**

Study	Study Type	Country	Dates	Participants	TTF	Controls	FU
Kesari et al (2017) <sup>13</sup>	EF-14 post hoc analysis	U.S., E.U., South Korea, Israel	2009-2016	204 patients with first recurrence in the EF-14 trial	144 patients treated with TTF plus second-line chemotherapy	60 patients treated with second-line chemotherapy	12.6 mo
Mrugala et al (2014) <sup>14</sup>	Registry	U.S. (91 centers)	2011-2013	457 patients with recurrent GBM	Patient Registry Dataset (PRiDe)	EF-11	

FU: follow-up; GBM: glioblastoma; TTF: tumor treating fields.



**Table 10. Summary of Key Nonrandomized Trial Results**

Study	Median OS, mo	Median OS With Bevacizumab, mo	
Kesari et al (2017) <sup>13</sup> ; EF-14			
TTF plus chemotherapy	11.8	11.8	
Chemotherapy alone	9.2	9.0	
Hazard ratio (95% CI)	0.70 (0.48 to 1.00)	0.61 (0.37 to 0.99)	
P value	0.049	0.043	
		1-Year OS, %	2-Year OS, %
Mrugala et al (2014) <sup>14</sup>			
PRiDe Registry	9.6	44	30
EF-11	6.6	20	9
Hazard ratio (95% CI)	0.66 (0.05 to 0.86)		
P value	<0.001		

CI: confidence interval; OS: overall survival, TTF: tumor treating fields.

Post hoc analyses of the EF-11 pivotal trial have been reported. Wong et al (2014) published a subgroup analysis to determine characteristics of responders and nonresponders in the active treatment and active treatment control.<sup>15</sup> They found that responders had a lower grade of histology and lower daily dexamethasone use than nonresponders. A second post hoc analysis by Kanner et al (2014) of the EF-11 pivotal trial data was performed to evaluate OS among patients who finished at least 1 complete course of TTF or chemotherapy.<sup>16</sup> The investigators reported that median OS was 7.7 months in the TTF group compared with 5.9 months in the chemotherapy group ( $p=0.009$ ). These post hoc analyses are considered to be hypothesis-generating.

#### **Section Summary: TTF Therapy as an Adjunct or Alternative to Chemotherapy for Progressive or Recurrent GBM**

The single RCT for TTF as an alternative to chemotherapy reported that outcomes following TTF therapy were similar to outcomes following standard chemotherapy. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. The noninferiority of TTF compared with chemotherapy might be considered a sufficient health benefit, if TTF reduced treatment toxicity. However, because the trial was not designed as a noninferiority trial no inferences of noninferiority compared with chemotherapy can be made. Physician's choice therapy during the trial was heterogenous, although analysis indicated that survival was not affected by choice of chemotherapy. More patients in the TTF group than in the control group did not complete the treatment course. The number of patients who contributed QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators might have been subject to bias due to the lack of blinding.

A nonrandomized post hoc evaluation of the EF-14 trial suggests that TTF may improve survival when combined with chemotherapy for recurrent GBM. This analysis should be considered hypothesis-generating, and further study in high-quality RCTs is needed.

#### **Summary of Evidence**

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes an RCT. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (i.e., temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.



For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

### Supplemental Information

#### Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests from Blue Cross Blue Shield Association, input was received from 3 physician specialty societies (one of which provided 6 responses and 2 of which provided 1 response each) and 1 academic medical center (total of 9 individual responses) in 2016. There was majority support, but not consensus, for the use of tumor treatment fields therapy as an adjunct to maintenance treatment following initial therapy for glioblastoma multiforme. There was mixed support for the use of tumor treatment fields as an alternative to chemotherapy in advanced or recurrent glioblastoma multiforme.

#### Practice Guidelines and Position Statements

National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2018) include recommendations for the treatment of glioblastoma (see Table 11).<sup>3</sup> For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate O<sup>6</sup>-methylguanine-DNA methyltransferase promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric field therapy is a category 1 recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a category 2B recommendation.

**Table 11. Guidelines for Adjuvant Treatment of Glioblastoma, by Age and Performance Status**

Age, y	KPS Score,%	Treatment Options	Category
≤70	≥60	<ul style="list-style-type: none"> <li>• Standard RT plus concurrent and adjuvant temozolomide plus TTF</li> <li>• Standard RT plus concurrent and adjuvant temozolomide</li> </ul>	1
≤70	<60	<ul style="list-style-type: none"> <li>• Hypofractionated RT with/without concurrent or adjuvant temozolomide</li> <li>• Temozolomide</li> <li>• Palliative/best supportive care</li> </ul>	2A
>70	≥60	<ul style="list-style-type: none"> <li>• Hypofractionated RT plus concurrent and adjuvant temozolomide</li> <li>• Standard RT plus concurrent and adjuvant temozolomide plus TTF</li> <li>• Temozolomide alone</li> <li>• Hypofractionated brain RT alone</li> </ul>	1
>70	<60	<ul style="list-style-type: none"> <li>• Hypofractionated brain RT alone</li> <li>• Temozolomide alone</li> </ul>	2A



Age, y	KPS Score,%	Treatment Options	Category
		• Palliative/best supportive care	

KPS: Karnofsky Performance Status; RT: radiotherapy; TTF: tumor treating fields.

#### U.S. Preventive Services Task Force Recommendations

Not applicable.

#### Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

#### Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 12. Of particular note are the phase 3 trials evaluating TTF therapy in non-small-cell lung cancer and pancreatic cancer. TTF therapy is an active area of research for mechanisms underlying its effects on cancer cells.

**Table 12. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
NCT01971281 <sup>a</sup>	A Phase II Study of TTFields (150 kHz) Concomitant With Gemcitabine and TTFields Concomitant With Gemcitabine Plus Nab-paclitaxel for Front-line Therapy of Advanced Pancreatic Adenocarcinoma	40	Dec 2017 (ongoing)
NCT01894061 <sup>a</sup>	A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma	40	Dec 2018
NCT02663271 <sup>a</sup>	A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFields and Pulsed Bevacizumab Treatment in Patients With Bevacizumab-refractory Recurrent Glioblastoma	18	Mar 2019
NCT02831959 <sup>a</sup>	Pivotal, Open-label, Randomized Study of Radiosurgery With or Without Tumor Treating Fields (TTFields) (150kHz) for 1-10 Brain Metastases From Non-small Cell Lung Cancer (NSCLC) (METIS)	270	Jul 2019
NCT02973789 <sup>a</sup>	LUNAR: Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields) Concurrent With Standard of Care Therapies for Treatment of Stage 4 Non-small Cell Lung Cancer (NSCLC) Following Platinum Failure	534	Dec 2021
NCT02743078 <sup>a</sup>	Phase II Trial Of Optune® Plus Bevacizumab In Bevacizumab-Refractory Recurrent Glioblastoma	85	Aug 2022
NCT03377491 <sup>a</sup>	EF-27 Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields, 150kHz) Concomitant With Gemcitabine and Nab-paclitaxel for Front-line Treatment of Locally-advanced Pancreatic Adenocarcinoma (PANOVA-3)	556	Dec 2022

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

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## Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Karnofsky Performance Score
  - Past and present diagnostic testing and results



- Previous treatment plan and response
- Tumor type and description
- Documentation of the patient's understanding on the use of the device
- Radiology report(s) and interpretation (i.e., MRI, CT scan, PET)

**Post Service**

- Results/reports of test performed

**Coding**

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.*

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

Type	Code	Description
CPT®	None	
HCPCS	A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
	E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type
ICD-10 Procedure	None	

**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
10/31/2014	BCBSA Medical Policy adoption	Medical Policy Committee
05/01/2016	Policy revision without position change	Medical Policy Committee
10/01/2016	Policy revision without position change	Medical Policy Committee
09/01/2017	Policy revision without position change	Medical Policy Committee
11/01/2018	Policy title change from Tumor Treatment Fields Therapy for Glioblastoma Policy revision with position change	Medical Policy Committee

**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance



with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

#### **Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*



## Medical Policy Reference Manual

### Medical Policy

#### 2.03.014 Electric Tumor Treatment Fields

Original MPC Approval: 04/05/2013

Last Review: 03/19/2018

Last Revision: 05/21/2018

#### Description

Glioblastoma multiforme (GBM) is the most common malignant primary intracranial tumor, with a median survival of only 10-14 months. Only 3% to 5% of patients survive more than 3 years. Recurrence is extremely common, which further decreases survival to 5-7 months. GBM is an aggressive tumor that presents treatment challenges owing to the resistance of the tumor cells to conventional therapies and the susceptibility of the brain to damage.

Electric tumor treatment fields (TTF) are low-intensity, intermediate frequency (100-200 kHz) alternating electric fields currently being explored as a possible method of improving survival in patients with GBM. The device consists of a portable electric field generator, a pair of electrodes, and accessories. The electrodes are placed on the patient's shaved scalp and current is applied at the prescribed frequency. The belief is that alternating electrical fields disrupt the rapidly dividing cancer cells, dislocating intracellular structures and leading to tumor cell death. Healthy brain tissue is not appreciably affected by the electrical current.

#### Policy

Electric tumor treating fields (TTF) is considered **medically necessary** for the treatment of histologically-confirmed glioblastoma (GBM) in patients 18 years of age and older.

Electric tumor treating fields (TTF) is considered **medically necessary** for patients that have completed debulking surgery or biopsy.

Electric tumor treating fields (TTF) is considered **medically necessary** for patients that have completed chemotherapy therapy and radiation therapy.

Electric tumor treating fields (TTF) is considered **medically necessary** when used concurrent with temozolomide (TMZ) for the treatment of GBM.

Electric tumor treating fields (TTF) is considered **experimental / investigational** for the treatment of any conditions not outlined above.

#### Policy Guidelines

1. The technology must have final approval from the appropriate government regulatory bodies:

The NovoTTF-100A system (Novocure, Ltd.) received a premarket approval (PMA) from the FDA in April 2011. According to the FDA approval document, "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with histologically confirmed glioblastoma multiforme (GBM), following histologically- or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted."



2. The scientific evidence must permit conclusions concerning the effect on health outcomes:

Pilot-level studies published since 2007 have shown mixed results. Overall when the primary end-point is taken to cancer survival the TTF treatment is similar to active chemotherapy, but quality of life analysis tends to favor the TTF treatment.

3. The technology must improve the net health outcome:

TTF therapy is still considered a novel treatment method, but with a high safety profile. The published evidence is not sufficient to determine net health outcomes.

4. The technology must be as effective as any established alternatives:

In terms of cancer survival, the evidence has not established that TTF treatment is at least as effective as the standard protocol.

5. The improvement must be attainable outside the investigational settings:

It is not known whether improvement can be expected outside of the investigational setting.

#### Update 2015:

A search of the peer-reviewed literature was performed for the period of March 2013 through October 2015. The NovoTTF-100A system's name was changed to Optune on September 28, 2014, based on a supplemental approval to the original PMA from the FDA. The newly approved, expanded FDA indications for the Optune is for treatment of adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune with temozolomide is intended for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

Electric tumor treatment fields for the treatment of GBM and other solid tumors continue to be evaluated in clinical trials. The policy statement is unchanged.

#### Update 2018:

A search of the peer-reviewed literature was performed for the period of November 2015 through January 2018. In 2015, Stupp et al published results of a randomized controlled trial (RCT) that evaluated both safety and efficacy of tumor-treating field (TTF) used in combination with temozolomide maintenance treatment after chemoradiation therapy for patients with glioblastoma multiforme (GBM). 695 patients were randomized in a 2:1 fashion to either receive maintenance treatment with TTF with temozolomide (TMZ) (n=466) or TMZ alone (n=229). Study eligibility required patients to be 18 years or older, have a histologically confirmed supratentorial glioblastoma, be progression-free after having undergone maximal safe debulking surgery when feasible or biopsy, and have completed standard concomitant chemoradiotherapy with TMZ. The median time from diagnosis to randomization was 3.8 months in both groups and patients were not blinded due to ethical concerns. TTF was delivered continuously (> 18 hours/day) via 4 transducers placed on the shaved scalp and TMZ (150-200 mg/m<sup>2</sup>/d) was given for 5 days of each 28-day cycle. Transducer array layouts were determined using the NvoTAL mapping software system for TTF fields to optimize field intensity within the treated tumor. A planned interim analysis was to be conducted on the first 315 patients at 18 months follow-up. The primary study endpoint was progression-free survival (PFS) in the intent-to-treat populations (with a significance threshold of p≤0.01) with overall survival (OS) in the per-protocol population (n = 280) as a powered secondary end point (significance threshold of .006). A total of 695 4 – DME85 patients were enrolled across 83 centers; however, the trial was terminated as it met its efficacy endpoints at interim analysis (median 38 months, 315 patients). The interim analysis included the planned 315 subjects, with 210 in the TTF/TMZ group and 105 in the TMZ only group. The analysis was conducted at a median 38 months follow-up (range, 18-60 months). Prespecified per-protocol median PFS in the TTF/TMZ group was 7.1 months (95% CI, 5.9- 8.2 months) compared to 4 months (95% CI, 3.3-5.2 months) in the TMZ only group (hazard ratio (HR), 0.62 [98.7% CI, 0.43-0.89]; P = .001). The median OS in the per-protocol population was statistically improved in the TTF/TMZ group (20.5 months; 95% CI, 16.7-25.0 months) compared to the TMZ only group (15.6 months; 95% CI, 13.3-19.1 months; HR, 0.64 [99.4% CI, 0.42-0.98]; P = .004). An additional analysis of the intention-to-treat population demonstrated and OS of 19.6 months (95% CI, 16.6-24.4 months) in the TTF/TMZ group compared to 16.6 months (95%CI, 13.6- 19.2months) in the TMZ only group (HR,0.74 [95% CI,0.56-0.98]; stratified log-rank p = .03). Forty-three percent of patients in the TTF/TMZ group were alive at 2-year follow-up, compared to 29% in the TMZ only group (p = .006).



The results of this study demonstrate an approximate three-month improvement of PFS and five-month improvement of OS when TTF therapy is used concurrently with TMZ in patients with newly diagnosed GBM.

## **Benefit Applications**

**Electric tumor treatment fields (TTF) services must be preauthorized for HMO members only.** Providers should submit preauthorization requests online at <https://provider.carefirst.com> or call 1-866-773-2884 (1-866-PRE-AUTH).

**Check the member's contract for benefits.**

NOTE: For FEP business, check the member's contract for benefits.

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**The following were among the resources reviewed and considered in developing this policy. By reviewing and considering the resources, CareFirst does not in any way endorse the contents thereof nor assume any liability or responsibility in connection therewith. The opinions and conclusions of the authors of these resources are their own, and may or may not be in agreement with those of CareFirst.**

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**This policy statement relates only to the services or supplies described herein. Coverage will vary from contract to contract and by line of business and should be verified before applying the terms of the policy.**



## Clinical Policy: Electric Tumor Treating Fields (Optune)

Reference Number: CP.MP.145

Last Review Date: 03/18

[Coding Implications](#)

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

### Description

Electric tumor treating fields (TTF), also known as alternating electric field therapy, are used for the treatment of glioblastoma, and are delivered by Optune<sup>®</sup> (NovoCure<sup>™</sup>), a portable medical device that generates low-intensity electric fields termed Tumor Treating Fields. TTF are believed to disrupt the rapid cell division exhibited by cancer cells, with the alternating electrical fields applied to the brain through electrodes placed on the scalp. The device is worn by the patient throughout the day and attached to the head by electrodes which creates a low intensity, alternating electric field within the tumor that exerts physical forces on electrically charged cellular components, preventing the normal mitotic process and causing cancer cell death prior to division.

### Policy/Criteria

- I. It is the policy of health plans affiliated with Centene Corporation<sup>®</sup> that TTF therapy is **medically necessary** for the following indication:
  - A. New diagnosis of glioblastoma, histologically confirmed, and all of the following:
    1. Glioblastoma is in the supratentorial region;
    2. Member has good performance status, as defined by a Karnofsky Performance Status rating of  $\geq 60$ ;
    3. Alternating electric field therapy will be delivered in conjunction with temozolomide after standard surgical and radiation therapies have been completed.
  - B. Recurrent glioblastoma, histologically- or radiologically- confirmed and all of the following:
    1. Glioblastoma is in the supratentorial region;
    2. Alternating electric field therapy will be used as a monotherapy, after standard treatment with surgery, radiation, and chemotherapy.
- II. It is the policy of health plans affiliated with Centene Corporation<sup>®</sup> that TTF therapy is **investigational and not medically necessary** for all other indications.
- III. It is the policy of health plans affiliated with Centene Corporation<sup>®</sup> that computer mapping software (NovoTal<sup>™</sup>) for planning TTF therapy is **investigational and not medically necessary** for all indications, as there is insufficient evidence to establish the efficacy of these products in the long-term outcomes of patients receiving TTF therapy.

### Background

#### *Optune Product Description<sup>1</sup>*

Optune, formerly NovoTTF-100A produces alternating electrical fields within the human body that disrupt the rapid cell division exhibited by cancer cells, with the alternating electrical fields applied to the brain through transducer arrays placed on the scalp. Electric TTF alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used for



a particular treatment is specific to the cell type being treated (e.g., 200kHz for GBM). In contrast, the TTF have not been shown to have an effect on cells that are not undergoing division. Since most normal adult brain cells proliferate very slowly, if at all, they are hypothesized to be little affected by the TTF. Testing demonstrates no differences between treated and control animals in histology of the major internal organs (including the brain), blood examination, cardiac rhythm, body temperature, or in animal behavior. In addition, because the fields alternate so rapidly, they have no effect on normal quiescent cells nor do they stimulate nerves and muscles. It is noted that, because TTF are only applied to the brain, they have no effect on rapidly proliferating cells in the rest of the body. The intensities of the electric fields within the tissues are very small and do not result in any meaningful increase in tissue temperature. Thus, TTF application has the advantage of being highly selective and is not expected to be associated with significant toxicity.

#### *Position Statement*

Guidelines from the National Comprehensive Cancer Network (NCCN) on central nervous system cancers, recommend alternating electrical fields therapy as a treatment option for newly diagnosed glioblastoma (2A- uniform consensus, based on low-quality evidence). The NCCN guidelines state TTF is recommended “for patients with good performance status and either methylated or unmethylated/indeterminate MGMT promoter status,” in conjunction with standard brain radiation therapy plus concurrent temozolomide and adjuvant temozolomide.<sup>2</sup> For recurrent glioblastoma, NCCN gives alternating electrical field therapy a 2B rating (consensus based on low-quality evidence).<sup>2</sup>

#### *Evidence for Optune*

Initial FDA approval for recurrent glioblastoma was based on Stupp et al.’s 2012<sup>3</sup> phase III clinical trial that randomized 237 patients to chemotherapy-free treatment of NovoTTF (20-24h/day) versus active chemotherapy in the treatment of patients with recurrent glioblastoma<sup>5</sup>. Primary end-point was improvement of overall survival. Patients were randomized to TTF alone or active chemotherapy control. Responses were more common in the TTF arm (14% versus 9.6%, p=0.19) and TTF-related adverse events were mild. Quality of life analyses favored TTF therapy in most domains. The investigators concluded that no improvement in overall survival was demonstrated. However, efficacy and activity with this chemotherapy-free treatment device appears comparable to chemotherapy regimens that are commonly used for recurrent glioblastoma. Toxicity and quality of life measures favored TTF.

The FDA based its approval<sup>4</sup> of the newly diagnosed glioblastoma indication of the Optune device on results from a 2015 clinical trial by Stupp et al.<sup>5</sup>. The EF-14 trial included 695 patients newly diagnosed with GB, and compared those who used Optune with temozolomide to those receiving temozolomide alone. Patients who used the device along with temozolomide lived, on average, about seven months with no disease progression compared to four months for those who had the drug alone. The Optune plus temozolomide group survived for an average of 19.4 months after starting treatment compared to 16.6 months for those who were treated with only temozolomide<sup>5</sup>. One critique of this study is that the study was terminated at the pre-planned intermediate analysis due to success of the TTF treatment. With the newly diagnosed glioblastoma indication, Optune can be used for GBM before the disease progresses. For newly



diagnosed GBM, Optune is not intended to be used as a substitute for standard treatments, but rather as an adjunct therapy, and should not be used without a physician's supervision.

Hayes conducted a review of the available literature on TTF, noting that overall the body of evidence was of fair to very poor quality, although it was consistently positive.<sup>6</sup> Hayes found the evidence to be stronger for the use of TTF for recurrent disease as opposed to newly diagnosed disease, as there were more supportive studies for recurrent disease at the time of publication (2 vs. 6). Out of the 10 studies they reviewed, pertaining to the use of TTF in patients with GBM and select other cancers, two were of fair quality, and the other eight ranged from poor quality to very poor quality. The two fair quality trials were those conducted by Stupp et al. in 2012<sup>5</sup> and 2015<sup>4</sup>, although these were noted to have limitations such as lack of a sham intervention and significant loss to follow up (22% and 20%, respectively)<sup>6</sup>.

A post-hoc analysis of Stupp et al.'s E-14 trial of TTF plus temozolomide versus temozolomide alone in newly diagnosed glioblastoma compared the efficacy of TTF plus physician's choice of chemotherapy versus chemotherapy alone after first recurrence<sup>7</sup>. Median overall survival in the TTF plus chemotherapy was 11.8 months versus 9.2 months for the chemotherapy only group ( $p=.049$ )<sup>7</sup>. TTF demonstrated low toxicity, consistent with previous studies. Limitations of this analysis are its post-hoc nature, as well as the crossover of 13 patients from the temozolomide only group to the TTF plus chemo group after approval and commercial availability of TTF for recurrent GBM<sup>7</sup>.

Vymazal et al.<sup>8</sup> analyzed the response patterns in individuals who exhibited an objective response to TTF in two previous studies in order to evaluate the baseline characteristics of those individuals who responded and to evaluate the relationship between compliance with use and efficacy outcomes. The analysis was completed on one pilot study ( $n=10$ ) and a phase III trial ( $n=237$ ) in which TTF was compared to standard chemotherapy. Between both studies, TTF was administered as monotherapy in 130 individuals. Across both trials, there was a 15% response rate (16/110 with a 4% complete response rate)<sup>8</sup>. There were no significant differences in baseline characteristics between the responder and nonresponder groups. In those in which a response was noted, there was frequently a delayed response; the tumor would initially continue to grow before responding to treatment. Analysis supported that an increase in compliance was associated with better treatment response and longer OS. The extent of treatment response in those who exhibited a response was dependent on compliance ( $p<0.001$ )<sup>8</sup>.

Although Optune is promising for the treatment of newly diagnosed glioblastoma, there is insufficient evidence to promote it as standard of care at this time. Evidence is stronger for recurrent glioblastoma which has been previously treated with radiation, surgery and chemotherapy.

#### *NovoTal*

The NovoTal system (Novocure) is a computer software planning tool that helps direct placement of transducer arrays for TTF therapy. Few studies have evaluated outcomes of TTF planned by physicians with and without the use of NovoTal, and these are limited to a case series, physician use study, and two review articles. Additionally, many of the authors reported ties to Novocure.



**Coding Implications**

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPSC Codes	Description
A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type

**ICD-10-CM Diagnosis Codes that Support Coverage Criteria**

ICD-10-CM Code	Description
C71.0 - C71.9	Malignant neoplasm of brain [supratentorial glioblastomas (WHO grade IV astrocytomas)]

Reviews, Revisions, and Approvals	Date	Approval Date
Policy adopted from Health Net Electric Tumor Treating fields policy.	04/17	05/17
Added new diagnosis of glioblastoma as medically necessary.	06/17	06/17
References reviewed and updated. Background updated. Codes reviewed.	03/18	03/18

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### **Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.



## CLINICAL POLICY

### Electric Tumor Treating fields



This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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**Note: For Medicaid members,** when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

**Note: For Medicare members,** to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

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# Medical Coverage Policy

Effective Date..... 7/15/2018  
 Next Review Date..... 3/15/2019  
 Coverage Policy Number ..... 0504

## Omnibus Codes

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### Related Coverage Resources

[Computerized Electrocardiograph \(ECG\) Analysis](#)  
[Deep Brain and Motor Cortex and Responsive](#)  
[Cortical Stimulation](#)  
[Nerve Conduction, Neuromuscular Junction, and](#)  
[Electromyography Testing](#)  
[Serological Testing for Inflammatory Bowel Disease](#)  
[Somatosensory Evoked Potentials](#)

#### INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

### Coverage Policy

#### [High Resolution Anoscopy \(CPT Codes 46601, 46607\)](#)

**High resolution anoscopy (HRA) is considered medically necessary for diagnosis of EITHER of the following:**

- suspicious anal lesion, including high-grade suspicious intraepithelial lesion (HSIL)
- anal dysplasia found in prior cytology/biopsy

**HRA for any other indication is considered experimental, investigational and unproven.**



#### Whole Body and Selective Head Hypothermia (CPT code 99184)

Whole body or selective head therapeutic hypothermia in a neonate  $\leq 28$  days of age is considered medically necessary for the treatment of moderate or severe hypoxic ischemic encephalopathy.

Whole body or selective head therapeutic hypothermia in a neonate  $\leq 28$  days of age for any other indication is considered experimental, investigational or unproven.

#### Tumor Treatment Fields (TTF) Therapy (HCPCS Codes A4555, E0766, 64999)

TTF therapy (i.e., Optune™) is considered medically necessary for individual 22 years of age or older with presence of histologically-confirmed glioblastoma multiforme (GBM) when EITHER of the following criteria are met:

- with confirmed recurrence after receiving chemotherapy and the device is being used as a monotherapy
- for adjuvant therapy with temozolomide

TTF (i.e., Optune™) for any other indication is considered experimental, investigational or unproven.

The use of treatment planning software (i.e., NovoTAL) (CPT code 64999) for use with tumor treatment fields for any indication, is considered experimental, investigational or unproven.

#### Insertion of Ocular Telescope Prosthesis Including Crystalline Lens (CPT Code 0308T, HCPCS Code C1840)

Intraocular telescope (Implantable Miniature Telescope [IMT]) is considered as medically necessary for an individual 65 years of age or older when ALL of the following criteria are met:

- with stable severe to profound vision impairment (best corrected distance visual acuity 20/160 to 20/800) caused by bilateral central scotomas associated with end-stage age-related macular degeneration (AMD)
- has retinal findings of geographic atrophy or disciform scar with foveal involvement, as determined by fluorescein angiography
- has evidence of visually significant cataract ( $\geq$  grade 2)
- agrees to undergo pre-surgery training and assessment (two to four visits) with low vision specialists (e.g., optometrist or occupational therapist) in the use of an external telescope
- achieve at least a 5-letter improvement on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart with an external telescope on the eye scheduled for surgery
- have adequate peripheral vision in the eye not scheduled for surgery
- agree to participate in postoperative visual training with a low vision specialist

### **EXPERIMENTAL, INVESTIGATIONAL OR UNPROVEN**

#### MarginProbe® (CPT Code 19499)

MarginProbe (CPT code 19499) for any indication is considered experimental, investigational or unproven.

#### Conjunctival Incision with Posterior Extrasccleral Placement of a Pharmacological Agent (CPT Code 68399)

Conjunctival incision with posterior extrasccleral placement of a pharmacological agent (CPT Code 68399) for any indication is considered experimental, investigational or unproven.



**Multivariate Analysis of Patient Specific Findings with Quantifiable Computer Probability Assessment (CPT Code 99199)**

Multivariate analysis of patient specific findings with quantifiable computer probability assessment (CPT code 99199) is considered experimental, investigational or unproven.

**Suprachoroidal Delivery of Pharmacological Agent (CPT Code 67299)**

Suprachoroidal delivery of pharmacological agent (CPT code 67299) is considered experimental, investigational or unproven.

**OTHER EXPERIMENTAL, INVESTIGATIONAL OR UNPROVEN SERVICES**

Each of the following services for any indication is considered experimental, investigational or unproven:

CPT®* Codes	Description	Comment
<a href="#">32994</a>	Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging guidance when performed, unilateral; cryoablation	
<a href="#">33340</a>	Percutaneous transcatheter closure of the left atrial appendage with endocardial implant, including fluoroscopy, transseptal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, when performed, and radiological supervision and interpretation	
<a href="#">34806</a>	Transcatheter placement of wireless physiologic sensor in aneurysmal sac during endovascular repair, including radiological supervision and interpretation, instrument calibration, and collection of pressure data (List separately in addition to code for primary procedure)	
<a href="#">34839</a>	Physician planning of a patient-specific fenestrated visceral aortic endograft requiring a minimum of 90 minutes of physician time	
<a href="#">34841</a>	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including one visceral artery endoprosthesis (superior mesenteric, celiac or renal artery)	
<a href="#">34842</a>	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including two visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
<a href="#">34843</a>	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including three visceral artery	



	endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
<a href="#">34844</a>	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including four or more visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
<a href="#">34845</a>	Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including one visceral artery endoprosthesis (superior mesenteric, celiac or renal artery)	
<a href="#">34846</a>	Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including two visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
<a href="#">34847</a>	Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including three visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
<a href="#">34848</a>	Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including four or more visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
<a href="#">46999</a>	Unlisted procedure, anus	Considered Experimental/Investigational/ Unproven when used to report transanal radiofrequency therapy for fecal Incontinence (e.g., SECCA procedure)
<a href="#">58674</a>	Laparoscopy, surgical, ablation of uterine fibroid(s) including intraoperative ultrasound guidance and monitoring, radiofrequency	
<a href="#">64999</a>	Unlisted procedure, nervous system	Considered Experimental/Investigational/



		Unproven when used to report implantation of trial or permanent electrode arrays or pulse generators for peripheral subcutaneous field stimulation
<a href="#">83993</a>	Calprotectin, fecal	
<a href="#">84999</a>	Unlisted chemistry procedure	Considered Experimental/Investigational/Unproven when used to report Holotranscobalamin, quantitative (Holtranscobalamin Testing)
<a href="#">88749</a>	Unlisted in vivo (eg, transcutaneous) laboratory service	Considered Experimental/Investigational/Unproven when used to report skin advanced glycation endproducts measurement by multi-wavelength fluorescent spectroscopy
<a href="#">91112</a>	Gastrointestinal transit and pressure measurement, stomach through colon, wireless capsule, with interpretation and report	
<a href="#">91299</a>	Unlisted diagnostic gastroenterology procedure	Considered Experimental/Investigational/Unproven when used to report 13C-Spirulina Gastric Emptying Breath Test (GEBT)
<a href="#">92978</a>	Endoluminal imaging of coronary vessel or graft using intravascular (IVUS) or optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; initial vessel (List separately in addition to code for primary procedure)	Considered Experimental/Investigational/Unproven when used to report CPT code 92978 using endoluminal imaging of coronary vessel or graft using optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; initial vessel
<a href="#">92979</a>	Endoluminal imaging of coronary vessel or graft using intravascular (IVUS) or optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; each additional vessel (List separately in addition to code for primary procedure)	Considered Experimental/Investigational/Unproven when used to report CPT code 92979 using endoluminal imaging of coronary vessel or graft using optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; each additional



		vessel
<a href="#">93702</a>	Bioimpedance spectroscopy (BIS), extracellular fluid analysis for lymphedema assessment(s)	
<a href="#">93799</a>	Unlisted cardiovascular service or procedure	Considered Experimental/Investigational/Unproven when used to report acoustic cardiography
<a href="#">93982</a>	Noninvasive physiologic study of implanted wireless pressure sensor in aneurysmal sac following endovascular repair, complete study including recording, analysis of pressure and waveform tracings, interpretation and report (Code deleted 12/31/2017)	
<a href="#">94799</a>	Unlisted pulmonary service or procedure	Considered Experimental/Investigational/Unproven when used to report intermittent measurement of wheeze rate for bronchodilator or bronchial challenge diagnostic evaluation
<a href="#">95999</a>	Unlisted neurological or neuromuscular diagnostic procedure	Considered Experimental/Investigational/Unproven when used to report tremor measurement with accelerometer(s) and/or gyroscope(s)
<a href="#">99199</a>	Unlisted special service, procedure or report	Considered Experimental/Investigational/Unproven when used to report near-infrared guidance for vascular access requiring real-time digital visualization of subcutaneous vasculature for evaluation of potential access sites and vessel patency
<a href="#">0100T</a>	Placement of a subconjunctival retinal prosthesis receiver and pulse generator, and implantation of intra-ocular retinal electrode array, with vitrectomy	
<a href="#">0106T</a>	Quantitative sensory testing (QST), testing and interpretation per extremity; using touch pressure stimuli to assess large diameter sensation	
<a href="#">0107T</a>	Quantitative sensory testing (QST), testing and interpretation per extremity; using vibration stimuli to assess large diameter fiber sensation	
<a href="#">0108T</a>	Quantitative sensory testing (QST), testing and interpretation per extremity; using cooling stimuli to assess small nerve fiber sensation and hyperalgesia	
<a href="#">0109T</a>	Quantitative sensory testing (QST), testing and interpretation per extremity; using heat-pain stimuli to assess small nerve fiber sensation and hyperalgesia	
<a href="#">0110T</a>	Quantitative sensory testing (QST), testing and interpretation per extremity; using other stimuli to assess sensation	
<a href="#">0174T</a>	Computer aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician	



	review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed concurrent with primary interpretation (List separately in addition to code for primary procedure)	
<a href="#">0175T</a>	Computer aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed remote from primary interpretation	
<a href="#">0190T</a>	Placement of intraocular radiation source applicator (List separately in addition to primary procedure)	
<a href="#">0205T</a>	Intravascular catheter-based coronary vessel or graft spectroscopy (eg, infrared) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation, and report, each vessel (List separately in addition to primary procedure)	
<a href="#">0207T</a>	Evacuation of meibomian glands, automated, using heat and intermittent pressure, unilateral	
<a href="#">0208T</a>	Pure tone audiometry (threshold), automated; air only	
<a href="#">0209T</a>	Pure tone audiometry (threshold), automated; air and bone	
<a href="#">0210T</a>	Speech audiometry threshold, automated	
<a href="#">0211T</a>	Speech audiometry threshold, automated with speech recognition	
<a href="#">0212T</a>	Comprehensive audiometry threshold evaluation and speech recognition (0209T, 0211T combined), automated	
<a href="#">0234T</a>	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; renal artery	
<a href="#">0235T</a>	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; visceral artery (except renal), each vessel	
<a href="#">0236T</a>	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; abdominal aorta	
<a href="#">0237T</a>	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; brachiocephalic trunk and branches, each vessel	
<a href="#">0238T</a>	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; iliac artery, each vessel	
<a href="#">0254T</a>	Endovascular repair of iliac artery bifurcation (eg, aneurysm, pseudoaneurysm, arteriovenous malformation, trauma, dissection) using bifurcated endograft from the common iliac artery into both the external and internal iliac artery, including all selective and/or nonselective catheterization(s) required for device placement and all associated radiological supervision and interpretation, unilateral	
<a href="#">0255T</a>	Endovascular repair of iliac artery bifurcation (eg, aneurysm, pseudoaneurysm, arteriovenous malformation, trauma) using bifurcated endoprosthesis from the common iliac artery into both the external and internal iliac artery, unilateral; radiological supervision and interpretation (Code deleted 12/31/2017)	
<a href="#">0266T</a>	Implantation or replacement of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intraoperative interrogation, programming, and repositioning, when performed)	



<a href="#">0267T</a>	Implantation or replacement of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming and repositioning, when performed)	
<a href="#">0268T</a>	Implantation or replacement of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)	
<a href="#">0269T</a>	Revision or removal of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)	
<a href="#">0270T</a>	Revision or removal of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)	
<a href="#">0271T</a>	Revision or removal of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)	
<a href="#">0272T</a>	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (eg, battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day);	
<a href="#">0273T</a>	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (eg, battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day); with programming	
<a href="#">0291T</a>	Intravascular optical coherence tomography (coronary native vessel or graft) during diagnostic evaluation and/or therapeutic intervention, including imaging supervision, interpretation, and report; initial vessel (List separately in addition to primary procedure) (Code deleted 12/31/2016)	
<a href="#">0293T</a>	Insertion of left atrial hemodynamic monitor; complete system, includes implanted communication module and pressure sensor lead in left atrium including transseptal access, radiological supervision and interpretation, and associated injection procedures, when performed (Code deleted 12/31/2017)	
<a href="#">0294T</a>	Insertion of left atrial hemodynamic monitor; pressure sensor lead at time of insertion of pacing cardioverter-defibrillator pulse generator including radiological supervision and interpretation and associated injection procedures, when performed (List separately in addition to primary procedure) (Code deleted 12/31/2017)	
<a href="#">0337T</a>	Endothelial function assessment, using peripheral vascular response to reactive hyperemia, non-invasive (eg, brachial artery ultrasound, peripheral artery tonometry), unilateral or bilateral	
<a href="#">0338T</a>	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed;	



	unilateral	
<a href="#">0339T</a>	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; bilateral	
<a href="#">0340T</a>	Ablation, pulmonary tumor(s), including pleura or chest wall when involved by tumor extension, percutaneous, cryoablation, unilateral, includes imaging guidance (Code deleted 12/31/2017)	
<a href="#">0341T</a>	Quantitative pupillometry with interpretation and report, unilateral or bilateral	
<a href="#">0342T</a>	Therapeutic apheresis with selective HDL delipidation and plasma reinfusion	
<a href="#">0351T</a>	Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; real-time intraoperative	
<a href="#">0352T</a>	Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; interpretation and report, real-time or referred	
<a href="#">0353T</a>	Optical coherence tomography of breast, surgical cavity; real-time intraoperative	
<a href="#">0354T</a>	Optical coherence tomography of breast, surgical cavity; interpretation and report, real-time or referred	
<a href="#">0378T</a>	Visual field assessment, with concurrent real time data analysis and accessible data storage with patient initiated data transmitted to a remote surveillance center for up to 30 days; review and interpretation with report by a physician or other qualified health care professional	
<a href="#">0379T</a>	Visual field assessment, with concurrent real time data analysis and accessible data storage with patient initiated data transmitted to a remote surveillance center for up to 30 days; technical support and patient instructions, surveillance, analysis, and transmission of daily and emergent data reports as prescribed by a physician or other qualified health care professional	
<a href="#">0380T</a>	Computer-aided animation and analysis of time series retinal images for the monitoring of disease progression, unilateral or bilateral, with interpretation and report	
<a href="#">0381T</a>	External heart rate and 3-axis accelerometer data recording up to 14 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional	
<a href="#">0382T</a>	External heart rate and 3-axis accelerometer data recording up to 14 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only	
<a href="#">0383T</a>	External heart rate and 3-axis accelerometer data recording from 15 to 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional	
<a href="#">0384T</a>	External heart rate and 3-axis accelerometer data recording from	



	15 to 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only	
<a href="#">0385T</a>	External heart rate and 3-axis accelerometer data recording more than 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional	
<a href="#">0386T</a>	External heart rate and 3-axis accelerometer data recording more than 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only	
<a href="#">0397T</a>	Endoscopic retrograde cholangiopancreatography (ERCP), with optical endomicroscopy (List separately in addition to code for primary procedure)	
<a href="#">0404T</a>	Transcervical uterine fibroid(s) ablation with ultrasound guidance, radiofrequency	
<a href="#">0408T</a>	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator with transvenous electrodes	
<a href="#">0409T</a>	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator only	
<a href="#">0410T</a>	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; atrial electrode only	
<a href="#">0411T</a>	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; ventricular electrode only	
<a href="#">0412T</a>	Removal of permanent cardiac contractility modulation system; pulse generator only	
<a href="#">0413T</a>	Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular)	
<a href="#">0414T</a>	Removal and replacement of permanent cardiac contractility modulation system pulse generator only	
<a href="#">0415T</a>	Repositioning of previously implanted cardiac contractility modulation transvenous electrode, (atrial or ventricular lead)	
<a href="#">0416T</a>	Relocation of skin pocket for implanted cardiac contractility modulation pulse generator	
<a href="#">0417T</a>	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, implantable cardiac contractility modulation system	
<a href="#">0418T</a>	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter; implantable cardiac contractility modulation system	
<a href="#">0465T</a>	Suprachoroidal injection of a pharmacologic agent (does not include supply of medication)	



<a href="#">0472T</a>	Device evaluation, interrogation, and initial programming of intraocular retinal electrode array (eg, retinal prosthesis), in person, with iterative adjustment of the implantable device to test functionality, select optimal permanent programmed values with analysis, including visual training, with review and report by a qualified health care professional	
<a href="#">0473T</a>	Device evaluation and interrogation of intraocular retinal electrode array (eg, retinal prosthesis), in person, including reprogramming and visual training, when performed, with review and report by a qualified health care professional	
<a href="#">0493T</a>	Near-infrared spectroscopy studies of lower extremity wounds (eg, for oxyhemoglobin measurement)	

HCPSC Codes	Description
<a href="#">C1841</a>	Retinal prosthesis, includes all internal and external components
<a href="#">C1842</a>	Retinal prosthesis, includes all internal and external components; add-on to C1841
<a href="#">C2624</a>	Implantable wireless pulmonary artery pressure sensor with delivery catheter, including all system components
<a href="#">C9741</a>	Right heart catheterization with implantation of wireless pressure sensor in the pulmonary artery, including any type of measurement, angiography, imaging supervision, interpretation, and report
<a href="#">E2120</a>	Pulse generator system for tympanic treatment of inner ear endolymphatic fluid
<a href="#">G0255</a>	Current perception threshold/sensory nerve conduction test, (sNCT) per limb, any nerve
<a href="#">S2103</a>	Adrenal tissue transplant to brain

\*Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.

## Overview

This Coverage Policy addresses multiple services and procedures.

## General Background

### Subsections:

[Services without Food and Drug Administration \(FDA\) Approval](#)

[Cardiovascular](#)

[Pulmonary](#)

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[Obstetrics/Gynecology](#)

[Ophthalmology](#)

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[Otolaryngology](#)

[Other](#)

### Services without Food and Drug Administration (FDA) Approval

This policy discusses the safety and effectiveness of certain technologies, services, and procedures, including those represented by some Category III CPT® codes. Category III codes are temporary codes that allow for data collection for these services/procedures.

Additionally, there are certain codes, including mainly Category III codes that represent services which have not yet received Food and Drug Administration (FDA) approval:



CPT®* Codes	Description	Comment
88749	Unlisted in vivo (eg, transcutaneous) laboratory service	Considered Experimental/Investigational/ Unproven when used to report skin advanced glycation endproducts measurement by multi-wavelength fluorescent spectroscopy
0190T	Placement of intraocular radiation source applicator (List separately in addition to primary procedure)	
0293T	Insertion of left atrial hemodynamic monitor; complete system, includes implanted communication module and pressure sensor lead in left atrium including transseptal access, radiological supervision and interpretation, and associated injection procedures, when performed (Code deleted 12/31/2017)	
0294T	Insertion of left atrial hemodynamic monitor; pressure sensor lead at time of insertion of pacing cardioverter-defibrillator pulse generator including radiological supervision and interpretation and associated injection procedures, when performed (List separately in addition to primary procedure) (Code deleted 12/31/2017)	
0338T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; unilateral	
0339T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; bilateral	
0342T	Therapeutic apheresis with selective HDL delipidation and plasma reinfusion	
0404T	Transcervical uterine fibroid(s) ablation with ultrasound guidance, radiofrequency	
0408T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator with transvenous electrodes	
0409T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator only	
0410T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; atrial electrode only	
0411T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; ventricular electrode only	



0412T	Removal of permanent cardiac contractility modulation system; pulse generator only	
0413T	Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular)	
0414T	Removal and replacement of permanent cardiac contractility modulation system pulse generator only	
0415T	Repositioning of previously implanted cardiac contractility modulation transvenous electrode, (atrial or ventricular lead)	
0416T	Relocation of skin pocket for implanted cardiac contractility modulation pulse generator	
0417T	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, implantable cardiac contractility modulation system	
0418T	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter; implantable cardiac contractility modulation system	

**\*Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.**

## **Cardiovascular**

### **Percutaneous transcatheter closure of the left atrial appendage (Codes 33340)**

Minimally invasive procedures for closure of the left atrial appendage (LAA) have been developed for the purpose of prevention of stroke. In an individual with atrial fibrillation (AF); it is a potential source for blood clots to form that lead to stroke. Percutaneous LAA closure devices are a nonpharmacologic alternative to anticoagulation for stroke prevention in AF. It is theorized that the devices may prevent thrombus formation and stroke by occluding the LAA.

The Watchman™ Left Atrial Appendage Closure Device (Boston Scientific, Maple Grove, MN) is a self-expanding nickel-titanium system. Implantation is performed percutaneously with a catheter delivery system, with venous access and trans-septal puncture to enter the left atrium. After implantation of device, patients receive anticoagulation with warfarin or other agents for approximately one to two months. During this acute period of time, anticoagulation may be necessary due to risk of thrombus formation related to altered blood flow around the implant. Patients are monitored with transesophageal echocardiography to assess blood flow and complete LAA closure (LAAC). After this period, patients will receive antiplatelet agents (e.g., aspirin and/or clopidogrel) indefinitely.

Other available devices that have not received FDA approval for the use of LAA closure include:

- The Amplatzer™ Cardiac Plug (St. Jude Medical, Minneapolis, MN) is approved for LAAC in Europe. The device closes off the LAA in a manner similar to the Watchman. The technique for implanting this device is also similar to that of the Watchman™ system.
- The Lariat® Loop Applicator is a suture delivery device that is designed to close a variety of surgical wounds in addition to LAAC. The technical approach differs from that of the Watchman system. The Lariat suture loop ligates the LAA from the epicardial space, with assistance of catheters and balloons in the left atrium.

### **U.S. Food and Drug Administration (FDA)**

The Watchman LAA Closure Technology received FDA premarket approval March 2015. The approval notes that the device is indicated to reduce the risk of thromboembolism from the left atrial appendage (LAA) in patients with non-valvular atrial fibrillation who:

- are at increased risk for stroke and systemic embolism based on CHADS<sub>2</sub> (cardiac failure, hypertension, age ≥ 75 years, diabetes, stroke) or CHA<sub>2</sub>DS<sub>2</sub>-VASc<sup>1</sup> (congestive heart failure, hypertension, age ≥ 75



years, diabetes, stroke/transient ischemic attack/thromboembolism, vascular disease, aged 65 to 74 years, sex category [female]) scores and are recommended for anticoagulation therapy

- are deemed by their physicians to be suitable for warfarin
- have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin

Other devices that have not received FDA approval for the use of LAA closure include but are not limited to:

- The Amplatzer™ Cardiac Plug (St. Jude Medical, Minneapolis, MN) is approved for LAAC in Europe. The device closes off the LAA in a manner similar to the Watchman. The technique for implanting this device is also similar to that of the Watchman system.
- The Lariat® Loop Applicator (Sentreheart, Palo Alto, CA) is a suture delivery device that is designed to close a variety of surgical wounds in addition to LAAC. The Lariat Loop Applicator device did receive 510(k) marketing clearance from FDA in 2006 as suture delivery device, but does not have FDA approval as a LAA closure device. Its intended use is to facilitate suture placement and knot tying in surgical applications where soft tissues are being approximated or ligated with a pretied polyester suture. The technical approach differs from that of the Watchman system. The Lariat suture loop ligates the LAA from the epicardial space, with assistance of catheters and balloons in the left atrium.
- PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) device (Apriva Medical, Inc., Sunnyvale, CA, USA) is no longer in production.

### Literature Review

Saw et al. (2017) reported on a study to evaluate the safety and efficacy of WATCHMAN of 106 patients who underwent WATCHMAN implantation at four major Canadian centers. The indications for left atrial appendage (LAA) closure were CHADS<sub>2</sub> ≥ 1 or CHA<sub>2</sub> DS<sub>2</sub> -VASc ≥ 2, and a contraindication/intolerance to or failure on anticoagulation. Follow-up imaging was typically performed 1-6 months postprocedure. Procedural success was 97.2% (103 of 106): one device embolization (snared percutaneously); one implant failure due to inadequate LAA depth; and, one cardiac perforation requiring surgical repair before WATCHMAN implantation. The composite major safety event-rate was 1.9% (one death and one device embolization). Antithrombotic therapy postimplant included dual antiplatelet therapy in 76 of 103 (73.8%). The mean follow-up was 210±182 days; there were two transient ischemic attacks, with estimated 66% reduction in thromboembolic events relative to CHADS<sub>2</sub> predicted risk. This is a preliminary study of patients with contraindication/intolerance to anticoagulation. The authors note that the results should be confirmed in larger prospective registries and randomized trials in this patient population.

Huang et al. (2017) reported on a single center, prospective, observational study to evaluate the procedural feasibility, safety and 12-month outcomes of the WATCHMAN LAA Occlusion Device in 106 nonvalvular atrial fibrillation (NVAF) patients with high risk for stroke. There was follow-up at one, three, six and 12 months after discharge. A transesophageal echocardiograph was performed at 45 days after implantation. The procedural success rate was 94.3% (100/106), and the occlusion rate was 100.0% (100/100). There were one tamponade, one ischemic stroke, and eight minor pericardial effusions during hospitalization. In the 12-month follow-up period, two patients developed a thrombus layer on the device that resolved with additional anticoagulation: one with visible device-thrombus experienced transient ischemic stroke, and one had a hemorrhagic stroke with no deaths in the study. The overall survival rate was 100.0%, and non-major adverse event rate of 95.0% (95/100). In this study, the expected annual rate of ischemic stroke risk in these patients according to the CHA<sub>2</sub>DS<sub>2</sub>-VASc score was 4.0%, while the observed ischemic stroke rate was 2.0% per year. The authors note that large multi-center trials and long-term follow-up are needed to evaluate the safety and efficacy of this application.

Betts et al. (2017) reported on a retrospective study assessing the feasibility and long-term efficacy of left atrial appendage occlusion (LAAO) in 371 patients in eight centers in the United Kingdom. The device choice was Watchman in 63% of cases, Amplatzer Cardiac Plug in 34.7%, Lariat in 1.7%, and Coherex WaveCrest in 0.6%. The 343 patients who received an LAAO device were followed up for 24.7 ± 16.07 months. The overall procedure success was 92.5%, with major events in 3.5% of cases. A significant improvement in procedure success (from 89.2% to 95.7%; P = 0.018) and reduction of acute major complications (from 6.5% to 0.5%; P = 0.001) were observed between procedures in the first and the second half of the recruitment time. An annual 90.1% relative



risk reduction (RRR) for ischemic stroke, an 87.2% thromboembolic events RRR, and a 92.9% major bleeding RRR were observed, if compared with the predicted annual risks based on CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-Vasc, and HAS-BLED scores, respectively. The study was limited by retrospective nature and lack of randomization.

Chen et al. (2017) reported on a retrospective study was designed to compare the feasibility and safety of left atrial appendage closure (LAAC) in primary and secondary stroke preventions. The study included 122 non-valvular atrial fibrillation (AF) patients with CHA<sub>2</sub>DS<sub>2</sub>-VAsC  $\geq 1$  selected for percutaneous LAAC operations. Outcome observations of primary and secondary stroke preventions with Watchman devices were analyzed and compared with 68 for primary stroke prevention and 47 for secondary prevention (included in the secondary prevention group when they had previous histories of stroke/TIA or infarct foci identified by head CT/MRI scan). Trans-esophageal echocardiography (TEE) was performed at 45 days. Both the CHA<sub>2</sub>DS<sub>2</sub>-VAsC score and the HASBLED score were significantly higher in the secondary prevention group ( $4.09 \pm 1.06$  vs.  $1.93 \pm 1.09$  for CHA<sub>2</sub>DS<sub>2</sub>-VAsC and  $1.83 \pm 1.03$  vs.  $1.26 \pm 0.87$  for HASBLED,  $P < 0.01$ ). In both groups LAAC were achieved with high successful rate (98.53% in the primary prevention group and 100% in the secondary prevention group,  $P > 0.05$ ) and low complication rates. In median follow-up of 12 months, stroke rates were found to be at low level in both groups (1.47% in primary prevention group vs. 2.13% in secondary prevention group,  $P > 0.05$ ). Limitations of the study include the lack of comparator group, and that it is a retrospective study. The authors note that prospective clinical trials with larger sample size and longer follow-up period are needed to study the efficacy and safety of LAAC in secondary stroke preventions.

Sahay et al. (2017) reported on a network meta-analysis to assess the efficacy and safety of LAAC compared with other strategies for stroke prevention in patients with AF. The review included randomized controlled trials comparing warfarin with placebo, antiplatelet therapy (APT) or Non-vitamin K antagonist oral anticoagulants (NOAC) in patients with AF using meta-analysis guidelines. Two major trials of LAAC were also included and a network meta-analysis with indirect comparison was performed to compare the impact of LAAC on mortality, stroke/systemic embolism (SE) and major bleeding in relation to medical treatment. The network meta-analysis included 19 RCTs (87,831 patients) with AF receiving anticoagulants, APT, placebo or LAAC. Indirect comparison with network meta-analysis using warfarin as the common comparator revealed efficacy benefit that favored LAAC as compared with placebo (mortality: HR 0.38, 95% CI 0.22 to 0.67,  $p < 0.001$ ; stroke/SE: HR 0.24, 95% CI 0.11 to 0.52,  $p < 0.001$ ) and APT (mortality: HR 0.58, 95% CI 0.37 to 0.91,  $p = 0.0018$ ; stroke/SE: HR 0.44, 95% CI 0.23 to 0.86,  $p = 0.017$ ) and similar to NOAC (mortality: HR 0.76, 95% CI 0.50 to 1.16,  $p = 0.211$ ; stroke/SE: HR 1.01, 95% CI 0.53 to 1.92,  $p = 0.969$ ). LAAC showed comparable rates of major bleeding when compared with placebo (HR 2.33, 95% CI 0.67 to 8.09,  $p = 0.183$ ), APT (HR 0.75, 95% CI 0.30 to 1.88,  $p = 0.542$ ) and NOAC (HR 0.80, 95% CI 0.33 to 1.94,  $p = 0.615$ ). The authors note that the findings of this meta-analysis suggest that LAAC is superior to placebo and APT, and comparable to NOAC for preventing mortality and stroke or SE, with similar bleeding risk in patients with nonvalvular AF. In addition, they note that these results should be interpreted with caution and more studies are needed to further substantiate this advantage, in view of the wide CIs with some variables in the current meta-analysis.

Saw et al. (2017) reported on a study to evaluate the safety and efficacy of WATCHMAN device for left atrial appendage (LAA) closure in 106 patients with nonvalvular atrial fibrillation (AF) and contraindications to anticoagulation. Indications for LAA closure were CHADS<sub>2</sub>  $\geq 1$  or CHA<sub>2</sub> DS<sub>2</sub> -VAsC  $\geq 2$ , and a contraindication/intolerance to or failure on anticoagulation. Follow-up imaging was performed one to six months post-procedure. The mean age of patients was  $74.8 \pm 7.7$ , mean CHADS<sub>2</sub> score was  $2.8 \pm 1.2$ , CHA<sub>2</sub> DS<sub>2</sub> -VAsC score was  $4.3 \pm 1.5$ , and HASBLED score was  $3.2 \pm 1.2$ . Indications for LAA closure were prior bleeding 89.6% (87 major bleeding and 8 minor bleeding), 9.4% were deemed high risk for bleeding, and 0.9% with recurrent strokes on warfarin. Procedural success was 97.2% (103 of 106), with one device embolization, one implant failure due to inadequate LAA depth, and one cardiac perforation requiring surgical repair before WATCHMAN implantation. The composite major safety event-rate was 1.9% (1 death and 1 device embolization). Antithrombotic therapy post-implant included dual antiplatelet therapy in 76 of 103 (73.8%). Mean follow-up was  $210 \pm 182$  days; there were two transient ischemic attacks, with estimated 66% reduction in thromboembolic events relative to CHADS<sub>2</sub> predicted risk. The authors note that LAA closure with the WATCHMAN device for patients with nonvalvular AF and contraindications to OAC is safe and effective, and the results should be confirmed in larger prospective registries and randomized trials in this population.



Noelck et al. (2016) reported on a systematic review benefits and harms of surgical or percutaneous LAA exclusion procedures. The review included controlled clinical trials that assessed the effectiveness of percutaneous LAA exclusion procedures and to assess the harms of percutaneous LAA procedures cohort and registry studies with 50 or more patients were included. For percutaneous interventions, the review included two randomized controlled studies and 11 registry studies. The findings note that there is low-strength evidence that percutaneous LAA exclusion is associated with a similar risk of long-term stroke and mortality as continued oral anticoagulation therapy. The finding is based on trials of one device (Watchman) studied in patients without contraindications to oral anticoagulant therapy. Most patients who received the Watchman device were able to discontinue oral anticoagulant therapy after undergoing follow-up transesophageal echocardiography (TEE) showing persistent closure of the LAA at three to six months. The review found that there is moderate strength evidence that a substantial proportion of patients undergoing various percutaneous LAA exclusion procedures experienced serious periprocedural harms with insufficient evidence to determine whether factors such as operator experience, patient selection criteria, or choice of device can modify these risks. In addition, it was noted that there is insufficient data to assess the balance of benefits and harms of percutaneous LAA exclusion procedures in patients who are ineligible for long-term oral anticoagulation therapy.

Boersma et al. (2016) reported on peri-procedural outcomes of up to 30-days from the prospective, multicenter registry (EWOLUTION). Baseline/implant data were available for 1021 subjects with high risk of stroke and moderate-to-high risk of bleeding. The device was successfully deployed in 98.5% of patients with no flow or minimal residual flow achieved in 99.3% of the implanted patients. Thirty-one serious adverse events (SAEs) were noted in 28 subjects within 1 day of the procedure. The overall 30-day mortality rate was 0.7%. The most common SAE that occurred within 30 days of the procedure was major bleeding requiring transfusion. The incidence of SAEs within 30 days was lower for subjects deemed to be ineligible for oral anticoagulation therapy (OAT) compared with those eligible for OAT (6.5 vs. 10.2%,  $P = 0.042$ ). The study is limited by lack of randomization, and short term follow-up. Boersma et al. (2017) reported on one-year follow-up of the EWOLUTION trial. At one year, mortality was 9.8%, noted by the author that is reflected the advanced age and comorbidities in the population. Device thrombus was observed in 28 patients at routine TEE (3.7%) and was not correlated with the drug regimen ( $P = .14$ ). Ischemic stroke rate was 1.1% (relative risk 84% vs estimated historical data); the major bleeding rate was 2.6% and was predominantly (2.3%) nonprocedure/device related.

A noninferiority randomized, controlled trial (RCT) compared LAA closure with Watchman device to warfarin treatment in patients with non-valvular atrial fibrillation (NVAF), the PROTECT AF trial (Holmes, et al., 2009; Reddy, et al., 2013a; Reddy, et al. 2014). The trial included 707 patients, randomized 2:1, with the device group  $n=463$  and warfarin group  $n=244$  and a follow-up time was  $3.8 \pm 1.7$  years (Reddy et al., 2014). Inclusion criteria: age  $\geq 18$  years; paroxysmal, persistent, or permanent NVAF and eligible for warfarin treatment; and, CHADS<sub>2</sub> score  $\geq 1$ . In the Watchman group the device implanted under transesophageal echocardiography (TEE) guidance with concomitant warfarin and Aspirin (ASA) (81-325 mg/day) for 45 days, on day 45, warfarin stopped, clopidogrel (75 mg/day) started until six month visit and then only ASA continued. In the warfarin group warfarin treatment was provided with a target INR 2-3. The primary efficacy outcome was stroke, systemic embolization, or cardiovascular death. The primary safety outcome was a composite of major bleeding events and procedure-related complications. At mean follow-up of 3.8 years, there were 39 events in 463 pts (8.4%) in the device group for primary event per 100 patient/years (pt/yr), compared with 34 events in 244 patients (13.9%) for primary event rate of 3.8 in 100 pt/yr in warfarin group. In the primary efficacy outcome, there was a noninferiority  $>99\%$ , and in the primary safety endpoint a noninferiority  $>98\%$ . Complications included in the Watchman group: serious pericardial effusion (4.8%); major bleeding (4.8%); procedure related ischemic stroke (1.3%); device embolization (0.6%); and hemorrhagic stroke (0.6%). In the warfarin group: major bleeding (7.4%); and, hemorrhagic stroke (3.7%). This study demonstrated the noninferiority of LAA closure compared to warfarin treatment. The study was limited in that it included warfarin, but did not include a comparison with the newer anticoagulants. The study included patients with warfarin, but does not address the patients who are unable to take anticoagulants.

A noninferiority RCT of that compared LAA closure with Watchman device and long-term warfarin treatment in pts with NVAF, the PREVAIL study (Holmes, et al., 2014). The study included 407 patients (randomized 2:1); with 68 patients enrolled through roll-in process with the Watchman group,  $n=269$  and warfarin group,  $n=138$ . The follow-up time was a median of 12 months. The inclusion criteria included: NVAF; CHADS<sub>2</sub>  $\geq 2$  or 1 CHADS<sub>2</sub> plus 1 high-risk characteristic. In the Watchman group, the device was implanted guided by fluoroscopy and



TEE; post-implant patients were treated with warfarin and ASA for 45 days; TEE performed at 45 days, 6 months, and 12 months. Warfarin was discontinued if the day 45 TEE documented closure of LAA or residual peri-device flow <5 mm and no definite visible large thrombus on device; then clopidogrel 75 mg/day and ASA 81-325 mg/day was prescribed until six months when clopidogrel discontinued. In the warfarin group warfarin treatment was given with target INR 2.0-3.0. At 18 months, the rate of the first coprimary efficacy endpoint (composite of stroke, systemic embolism [SE], and cardiovascular/unexplained death) was 0.064 in the device group versus 0.063 in the control group and did not achieve the prespecified criteria noninferiority. The rate for the second coprimary efficacy endpoint (stroke or SE >7 days' post-randomization) was 0.0253 versus 0.0200 achieving noninferiority. Early safety events occurred in 2.2% of the Watchman arm. Complications (reported for Watchman-group only) (% of patients): device embolization (0.7%); arteriovenous fistula (0.4%); cardiac perforation (0.4%); pericardial effusion with cardiac tamponade (0.4%); major bleed requiring transfusion (0.4%). Noninferiority was not achieved for overall efficacy in this study. The patients in this study were required to be candidates for long-term anticoagulation to facilitate randomization against a control group treated with warfarin. The trial does not address the safety and efficacy of LAA occlusion when anticoagulation is contraindicated. In addition, the study does not include comparison with new oral anticoagulants.

Hayes published a technology assessment for the use of percutaneous LAA closure devices to reduce risk of stroke in patient with atrial fibrillation (AF) (Hayes 2015; 2016; 2017). It was noted that among the four studies that evaluated the efficacy of Watchman in stroke prevention in patients with non-valvular AF (NVAf), the 2 RCTs found this device to be noninferior compared with warfarin OAC in almost all primary measures. Both uncontrolled studies that compared observed versus expected stroke rates reported a lower observed rate in patients implanted with the Watchman device; however, neither study included a statistical test of significance. Regarding safety, LAA closure with the Watchman device is associated with a low but measurable risk of significant procedural/device-related complications such as major bleeding, pericardial effusion, stroke, device embolization, and cardiac perforation or tamponade. The conclusion included these findings regarding the Watchman device:

- Available evidence supports the use of the Watchman device for its FDA-approved indication in LAA closure.
- Since following implantation of the Watchman device patients must continue on warfarin therapy for approximately 45 days, there are very limited data on if and how to use the Watchman device in patients with absolute contraindications to warfarin.
- There would be a benefit from randomized studies that compare device-mediated LAA closure against treatment with the newer OACs and that test the use of the newer OACs as an adjunct to LAA closure.
- Trials are needed to help identify the patient subgroups that would most benefit from LAA closure.

#### **Professional Societies/Organizations**

##### **American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS):**

These organizations published joint guidelines for the management of patients with atrial fibrillation (January, et al., 2014). The guidelines include a discussion of percutaneous occlusion of the LAA but do not provide specific recommendations regarding the use of these devices.

**American Heart Association (AHA)/American Stroke Association (ASA):** Joint guidelines from these organizations for the primary prevention of stroke include the following recommendations regarding LAA closure (Meschia, et al., 2014):

- closure of the LAA may be considered for high-risk patients with AF who are deemed unsuitable for anticoagulation
- performed at a center with low rates of periprocedural complications
- the patient can tolerate the risk of at least 45 days of post-procedural anticoagulation

(Class IIb; Level of Evidence B)

Level of evidence B: limited populations evaluated. Data derived from a single randomized trial or nonrandomized studies.

Class IIb: recommendation's usefulness/efficacy less well established; greater conflicting evidence from single randomized trial or nonrandomized studies

#### **Use Outside of the US**



**Canadian Cardiovascular Society (CCS):** The CCS published guidelines for the management of atrial fibrillation (Verma, et al., 2014). The guidelines note the following regarding LAA closure devices:

- LAA closure devices are not currently approved for use in Canada.
- It is suggested that these non-approved LAA closure devices not be used, except in research protocols or in systematically documented use protocols in patients at high risk of stroke (CHADS<sub>2</sub> score  $\geq 2$ ) for whom antithrombotic therapy is precluded (Conditional Recommendation, Low-Quality Evidence).

**European Society of Cardiology (ESC):** The ESC published updated guidelines for management of atrial fibrillation (Kirchhof, et al., 2016). The guidelines noted:

Recommendations for occlusion or exclusion of the left atrial appendage:

- After surgical occlusion or exclusion of the LAA, it is recommended to continue anticoagulation in at-risk patients with AF for stroke prevention.

Class I\*

Level B

- LAA occlusion may be considered for stroke prevention in patients with AF and contra-indications for long-term anticoagulant treatment (e.g. those with a previous life-threatening bleed without a reversible cause).

Class IIb\*

Level B

- Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery.

Class IIb\*

Level B

- Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients undergoing thoracoscopic AF surgery.

Class IIb\*

Level B

\*Class of recommendations:

Class I - Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.

Class IIb - established by evidence/opinion. Usefulness/efficacy is less well established by evidence/opinion.

Level of evidence:

B Data derived from a single randomized clinical trial or large non-randomized studies.

**European Heart Rhythm Association (EHRA)/European Association of Percutaneous Cardiovascular Interventions (EAPCI):** EHRA/EAPCI published expert consensus statement on catheter-based left atrial appendage occlusion (Meier, et al., 2014). The statement includes the following:

- The main indication for LAA occlusion is AF with a CHADS<sub>2</sub> score  $\geq 1$  or CHA<sub>2</sub>-DS<sub>2</sub>-VASc score  $\geq 2$  and a relative or absolute contraindication to prolonged oral anticoagulation.
- Tolerance for at minimum several weeks of dual antiplatelet therapy, usually followed by lifelong single antiplatelet drug therapy.

**National Institute for Health and Care Excellence (NICE):** NICE clinical guidelines for the management of atrial fibrillation include the following recommendations regarding LAA closure (2010):

- Consider left atrial appendage occlusion (LAAO) if anticoagulation is contraindicated or not tolerated and discuss the benefits and risks of LAAO with the person.
- Do not offer LAAO as an alternative to anticoagulation unless anticoagulation is contraindicated or not tolerated.

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**Chronic baroreceptor stimulation of the carotid sinus (CPT codes 0266T, 0267T, 0268T, 0269T, 0270T, 0271T, 0272T, 0273T)**

The Barostim<sup>®</sup> neo implantable device (CVRx, Minneapolis, MN) is proposed to address cases of unmet treatment needs in patients with drug resistant hypertension. The Barostim neo device has replaced the Rheos Baroreflex Hypertension device. The device consists of an implantable pulse generator (IPG), one connecting lead wire, and an external wireless programmer system that allows physicians to modify device therapy. It is implanted under the skin beneath the collar bone with the lead positioned outside the carotid artery to conduct energy from the IPG to carotid baroreceptors. Activated baroreceptors signal the brain to respond to a rise in blood pressure. The brain responds by stimulating pathways of the autonomic nervous system responsible for arterial vessel dilation, heart rate, and fluid excretion. The device is also being investigated for use in heart failure.

**U.S. Food and Drug Administration (FDA)**

December 2014 the Barostim neo<sup>®</sup> Legacy System received humanitarian device exemption (HDE). The device is indicated for use in patients with resistant hypertension who have had bilateral implantation of the Rheos<sup>®</sup> Carotid Sinus Leads Models 1010R, 1010L, 1014L, and 1014R (which have been discontinued and are obsolete) and were determined responders in the Rheos<sup>®</sup> pivotal clinical study.

**Literature Review**

Wallbach et al. (2016) reported on a prospective study that evaluated ambulatory BP measurement (ABPM) data in patients with therapy-refractory hypertension (HTN) treated with the Baroreflex activation therapy (BAT) neo device. ABPM was performed before BAT implantation and six months after initiation of BAT. A total of 51 patients were included into this study, with seven dropping out from analysis. After six months, 24-hour ambulatory systolic (from 148 ± 17 mm Hg to 140 ± 23 mm Hg, P<0.01), diastolic (from 82 ± 13 mm Hg to 77 ± 15 mm Hg, P<0.01), day- and night-time systolic and diastolic BP (all P ≤ 0.01) decreased while the number of prescribed antihypertensive classes could be reduced from 6.5 ± 1.5 to 6.0 ± 1.8 (P=0.03). Heart rate and pulse pressure remained unchanged. BAT was equally effective in reducing ambulatory BP in all subgroups of patients. The authors note that randomized controlled trials are needed to evaluate BAT effects on ABPM in patients with resistant hypertension accurately. This study is limited by the small number of subjects and lack of randomization.

Biognano et al. (2011) published the pivotal study regarding Baroreflex activation therapy (BAT) of the Rheos device. Patients were randomized to receive either active BAT (group A, n=181) or deferred BAT (group B, n=84) with the Rheos system. Active BAT was initiated one month after implantation, while deferred BAT was started seven months after implantation. This design allowed short term comparison between BAT and medical management. The coprimary endpoints: 1) acute systolic blood pressure (SBP) responder rate at 6 months; 2) sustained responder rate at 12 months; 3) procedure safety; 4) BAT safety; and 5) device safety. At 6-month follow-up, 54% of active group patients and 45% of those not receiving active therapy achieved the preset acute efficacy goal of at least 10 mm Hg reduction in (SBP); between-group comparison was not statistically significant. The 30-day rate of procedure- or device-related serious adverse events was 25.5%, which did not meet the preset objective performance criterion (OPC) for procedural safety. Although the 12-month sustained efficacy endpoint was met, this endpoint was assessed by comparing Group A patient outcomes with OPC rather than with Group B outcomes, leading to difficulty in interpretation of the clinical relevance of this result. The long-term device safety and short-term BAT safety primary outcomes were met.



Following completion of the randomized Rheos Pivotal Trial, Bakris et al. (2012) conducted an open-label, nonrandomized single-arm follow-up to assess safety and efficacy of BAT. Blood pressure reductions were measured relative to a pre-implant baseline as well as the results achieved at the completion of 1 year of follow-up in the randomized phase. Clinically significant responder status was assessed according to FDA-mandated criteria. Of the 322 patients implanted, 76% (n=245) qualified as clinically significant responders, an additional 10% were indeterminate. Among long-term responders receiving BAT, the mean blood pressure drop was 35/16 mm Hg. Among responders, 55% achieved goal blood pressures (<140 mm Hg or <130 mm Hg in diabetes or kidney disease). Blood pressures of all active patients remained stable from completion of the randomized phase through long-term follow-up. BAT substantially reduced arterial pressure for most patients participating in the Rheos Pivotal Trial. This blood pressure reduction or goal achievement was maintained over long-term follow-up of 22 to 53 months.

#### Use Outside of the US

No relevant information

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**Endovascular Repair of Visceral Aorta for Abdominal Aortic Aneurysm (including planning) (CPT Codes 34806, 34839, 34841, 34842, 34843, 34844, 34845, 34846, 34847, 34848, 93982) (Codes 34806, 93982 deleted 12/31/2017)**

The conventional treatment for AAA has been open surgical repair. Open surgical repair involves transabdominal surgery, exposure of the aneurysm, cross-clamping the aorta, resection of the aneurysm, and placement of graft prosthesis. Endovascular AAA repair developed as a minimally invasive alternative to open surgical repair in patients with suitable anatomy. Endovascular repair of infrarenal abdominal or aortoiliac AAA has demonstrated reduced rates of perioperative mortality and morbidity compared to open surgical repair, with equivalent long-term aneurysm-related mortality, although this approach is associated with higher rates of reintervention, and requires long-term radiological monitoring. Endovascular repair may be a reasonable option for selected patients with suitable anatomy for whom the risk/benefit ratio favors endovascular repair.

The use of fenestrated grafts (e.g., Zenith® Fenestrated AAA Endovascular Graft) has been investigated for the treatment of patients with AAA involving the visceral arteries. These grafts include fenestrations, or scallops, in the graft material that allow the proximal edge of the material to be placed above the renal arteries while permitting blood flow to vessels accommodated by the fenestrations. Evidence published in the medical literature consists primarily of registry data, small feasibility studies, and case series with limited outcome data. Additional evidence is needed to determine the safety, efficacy, and long-term outcomes of this procedure and to determine how this approach compares to surgical repair.

**U.S. Food and Drug Administration (FDA)**

A number of devices have received approval through the FDA Premarket Approval (PMA) process for endovascular treatment of AAA, including the following:

- AneuRx® Stent Graft System (Medtronic Vascular, Santa Rosa, CA)
- Zenith® AAA Endovascular Graft and H&L-B One-Shot™ Introduction System (Cook Incorporated, Bloomington, IN)
- EXCLUDER™ Bifurcated Endoprosthesis (W.L. Gore & Associates, Inc., Flagstaff, AZ)
- Endologix PowerLink® System (Endologix, Inc., Irvine, CA).
- Talent™ Abdominal Stent Graft System (Medtronic Vascular, Santa Rosa, CA)
- Endurant Stent Graft System (Medtronic Vascular, Santa Rosa, CA)

The Zenith® Fenestrated AAA Endovascular Graft (with the adjunctive Zenith Alignment Stent) received FDA PMA approval on December 22, 2011. The Zenith graft is indicated for the endovascular treatment of patients with abdominal aortic or aortoiliac aneurysm having morphology suitable for endovascular repair, including:

- Adequate iliac/femoral access compatible with required introduction systems
- Nonaneurysmal infrarenal aortic segment (neck) proximal to the aneurysms with:
  - Length ≥ 4 mm and unsuitable for a non-fenestrated graft
  - Diameter ≤ 31 mm and ≥ 19 mm
  - Angle < 45 degrees relative to long axis of aneurysm
  - Angle < 45 degrees relative to axis of suprarenal aorta
- Ipsilateral iliac artery fixation site > 30 mm in length and between 9- 21 mm in diameter
- Contralateral iliac artery distal fixation site >30 mm in length and between 7 – 21 mm in diameter

The Zenith Alignment Stent is indicated for use as an adjunct to the Zenith Fenestrated AAA Endovascular Graft to secure positive alignment of fenestrations or scallops with the orifice of aortic branch vessels having diameters ranging from 3 to 8 mm. Unlike the standard Zenith AAA Endovascular Graft, the Zenith Fenestrated AAA graft has fenestrations or scallops in the graft material, which allow the proximal edge of graft material to be placed above the renal arteries while still permitting blood flow to vessels accommodated by the fenestrations or scallops. In order to account for anatomical variation, each proximal body graft is made to order for a specific patient. The Zenith fenestrated graft has been available outside the U.S. since 2002.

The CardioMEMS EndoSure™ Wireless AAA Pressure Measurement System was approved for marketing through the 510(k) process on October 12, 2006 for the measurement of intrasac pressure during endovascular



AAA repair and for use as an adjunctive tool in the detection of intraoperative leaks. In a subsequent approval on March 15, 2007, measurement of intrasac pressure during thoracic aortic aneurysm repair was added as an intended use.

According to the 510(k) summary, the sensor is implanted in the aneurysm sac during stent graft deployment and is left in place in the excluded portion of the aneurysm as a permanent implant. The main body of the sensor is composed of fused silica coated in silicone. Nitinol loops extend from and surround the sensor body. The sensor is interrogated using the antenna of the EndoSure Electronics System. Once the signal is acquired, a pressure waveform and numerical pressure data are displayed on the touch-screen, and a printout of the data and waveform is generated.

### Literature Review

Hayes published a technology directory report on endovascular repair of abdominal aortic aneurysms (AAA) (Hayes 2013; 2016; 2017). The review included 11 randomized controlled trials (RCTs). The RCTs of endovascular aneurysm repair (EVAR) indicate that outcomes are comparable with open surgery for large aneurysms in need of repair, with surveillance for small aneurysms, and with open surgery for the treatment of ruptured aneurysms. The six trials that compared EVAR with open surgery for unruptured AAAs generally found lower 30-day mortality rates with EVAR than with open surgery, but intermediate-term (one to four years) survival and long-term survival (5+ years) were not different between groups, which suggests that the benefit of EVAR occurs in the immediate postoperative period. Of the five studies that reported health-related quality of life (HRQL) results, three found an early benefit with EVAR that was not maintained past three to six months. Complication rates were not consistently different between groups, with the exception that reintervention rates were higher with EVAR than with open surgery in several trials. In the two RCTs that compared EVAR with surveillance for small unruptured AAAs, no differences were observed between groups in 30-day mortality or intermediate-term survival. One study found significantly higher HRQL scores in the EVAR group than in the surveillance group at six months, but the differences were nonsignificant as the study progressed with both studies stopped early based on futility analyses. In the single study that compared EVAR with no treatment for large unruptured AAAs in patients unfit for open surgery, 7% of patients died within 30 days due to EVAR procedure-related causes. No differences between groups were noted in survival or HRQL after up to four years of follow-up (median, 2.4 years), but complications were significantly higher in the EVAR group than in the surveillance group. Two small RCTs (32 and 116 patients) compared EVAR with open repair of ruptured AAA, but neither study found differences in 30-day mortality rates between groups or in overall rates of moderate or severe complications. Mortality rates also did not differ in the study that followed patients for up to two years. The review noted limitations of the RCTs that included the lack of blinding procedures for patients and assessors for many outcome measures. In addition, the studies included a preponderance of males; although no systematic differences in outcomes between men and women were apparent. The surgeries in these studies were performed by experienced surgical teams, and it is uncertain whether these results would generalize to groups with less experienced surgeons. Additionally, in the studies that included surveillance groups for small AAAs, screening procedures were required every six months to monitor AAA size and growth rate; it is therefore uncertain whether the results with the surveillance group would apply to patients with AAAs that are screened less frequently.

**Endovascular Repair Using a Fenestrated Graft:** The British Society for the Endovascular Therapy and the Global Collaborators on Advanced Stent-Graft Repair (GLOBALSTAR) Registry published early results of endovascular repair of juxtarenal aortic aneurysms using the Zenith fenestrated graft in the United Kingdom (2012). Data from 318 patients treated at 14 experienced centers (i.e., > 10 procedures) were retrospectively studied. The primary procedural success rate was 99% (316/318); perioperative mortality was 4.1%; and intraoperative target vessel loss was observed in 5 of 889 target vessels (0.6%). The early reintervention rate (i.e., <30 days) was 7%. There were 11 deaths during the follow-up, but none were aneurysm-related. Freedom from target-vessel loss at one, two, and three years was 93%, 91%, and 85%, respectively, and freedom from late secondary intervention (> 30 days) was 90%, 86%, and 70% at one, two and three years, respectively. The authors stated that these results support continued use and evaluation of this technique for juxtarenal aneurysms, but illustrate the need for a more robust evidence base.

Amiot et al. (2010) conducted a retrospective analysis to evaluate the medium-term outcomes of aortic aneurysm repair using the Zenith fenestrated graft in 16 French academic centers (n=134). Patients were considered to be



at high risk for open surgical repair. The median aneurysm size was 56 mm (range 45-91 mm), and the median patient age was 73 years (range 43-91 years). A total of 403 visceral vessels were treated, including 265 renal arteries. One early conversion to surgery was required. Angiography immediately following the procedure demonstrated patency in 398 of 403 target vessels. The 30-day mortality was 2%. Imaging prior to discharge revealed 16 (12%) endoleaks (3 type I, 12 type II, and 1 type III). Transient or permanent dialysis was required in 4 (3%) and two (1%) patients, respectively. During a median follow-up of 15 months (range 2-53 months), no aneurysms ruptured or required open conversion. Aneurysm sac size decreased by more than 5 mm in 52%, 65.6%, and 75% of patients at one, two and three years, respectively. Three patients had sac enlargement within the first year associated with persistent endoleaks. Four renal artery occlusions were detected during follow-up, and 12 procedures related to reintervention were performed in 12 patients, including six to correct endoleaks and five to correct threatened visceral vessels. Twelve of 131 patients died during follow-up; none of these were aneurysm related.

Greenberg et al. (2009) reported intermediate results of a multicenter prospective case series to assess the safety and efficacy of the Zenith fenestrated devices (n=30) in patients with juxtarenal AAA. Inclusion criteria consisted of aortic or aortoiliac aneurysms with diameter greater than five cm, or with aortic or aortoiliac aneurysms with a history of growth greater than 0.5 cm per year or clinical indication for AAA repair. Customized devices were designed for each patient based on calculations derived from computed tomography (CT) scan data. A total of 77 visceral vessels were accommodated by fenestrations within the sealing segment of the grafts. The most common design accommodated two renal arteries and the superior mesenteric artery (66.7%). Prostheses were successfully implanted in all patients. Of the 30 patients, 27 were available for follow up at 12 months, and 23 were available at 24 months. There were no aneurysm related deaths, aneurysm ruptures, or conversions during the follow-up period. There were no type I or type III endoleaks reported. Type II endoleaks were reported in six patients (26.1%) at 12 months, and in four (20.0%) at 24 months. None of the patients had aneurysm growth > 5 mm. Aneurysm size at 24 months decreased in 16 of 23 patients (69.6%) and was stable in the remaining patients. A renal event occurred in eight patients. Secondary interventions were performed in five patients. No patients experienced renal failure requiring dialysis. The authors concluded that the intermediate term results of this multicenter study are concordant with previous single-center studies and support the concept the placement of fenestrated endovascular grafts is safe and effective at centers with experience in endovascular repair and renal/mesenteric stent placement.

An Agency for Healthcare Research and Quality (AHRQ) evidence report/technology assessment (Wilt et al., 2006) compared endovascular and open surgical repairs for AAA. Randomized controlled trials of open surgical repair, endovascular repair, or active surveillance; systematic reviews; nonrandomized U.S. trials; and national registries were used to assess clinical outcomes. The assessment concluded that for AAA < 5.5 cm in diameter, active surveillance with delayed open surgical repair results in equivalent mortality, but less morbidity, due to fewer interventions, compared to immediate open surgical repair. Endovascular repair of aneurysms ≥ 5.5 cm has not been shown to improve long-term survival or health status compared to open surgical repair, although perioperative outcomes are improved. The assessment also stated that endovascular repair does not improve survival in patients who are medically unfit for open surgical repair. Endovascular repair is associated with more complications, need for reintervention, and monitoring compared to open surgical repair or no intervention. The AHRQ report recommended U.S. randomized controlled trials be conducted with approved endovascular repair devices to evaluate patient outcomes.

**CardioMEMS EndoSure Wireless AAA Pressure Measurement System:** Published evidence on the use of the CardioMEMS system consists of several diagnostic cohort studies with short-term preliminary results (Hoppe et al., 2008, n=12; Silveira et al., 2008, n=25; Ohki et al., 2007, n=76). The safety and clinical utility of this technology in the intraoperative or long-term monitoring of patients following endovascular aortic aneurysm repair has not been established.

#### **Use Outside of the US**

No relevant information.

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**Endovascular repair of iliac artery bifurcation (CPT 0254T, 0255T) (Code 0255T deleted 12/31/2017, use 0254T to report):**

Involvement of the common iliac arteries occurs in approximately 20% of patients with abdominal aortic aneurysms (AAA) and may present a challenge to endovascular treatment since it may compromise sealing and distal fixation of endoprostheses. Several techniques have been developed to achieve the goal of sealing the aneurysmal sac, with one of the techniques is developed of an endoprosthesis for use in the iliac arteries. A device that has been developed exclusively for use in the iliac arteries is the GORE® EXCLUDER® Iliac Branch Endoprosthesis (IBE) (W. L. Gore & Associates, Inc., Flagstaff, AZ). It is intended to be used in conjunction with the Gore Excluder abdominal aortic aneurysm (AAA) endoprosthesis to isolate the common iliac artery from the systemic blood flow and is intended to preserve blood flow to the external and internal iliac arteries and preserve pelvic perfusion (Hayes, 2017).

**U.S. Food and Drug Administration (FDA)**



The GORE® EXCLUDER® Iliac Branch Endoprosthesis (IBE Device) received FDA premarket (PMA) approval February 2016. It is indicated for use with the GORE® EXCLUDER® AAA Endoprosthesis to isolate the common iliac artery from systemic blood flow and preserve blood flow in the external iliac and internal iliac arteries in patients with a common iliac or aortoiliac aneurysm, who have appropriate anatomy that includes:

- Adequate iliac/femoral access
- Minimum common iliac diameter of 17 mm at the proximal implantation zone of the IBE
- External iliac artery treatment diameter range of 6.5-25 mm and seal zone length of at least 10 mm
- Internal iliac artery treatment diameter range of 6.5-13.5 mm and seal zone length of at least 10 mm
- Adequate length from the lowest major renal artery to the internal iliac artery to accommodate the total endoprosthesis length, calculated by adding the minimum lengths of required components, taking into account appropriate overlaps between components

Contraindications to the device include:

- Patients with known sensitivities or allergies to the device materials. All components of the GORE EXCLUDER Iliac Branch Endoprosthesis and the GORE EXCLUDER AAA Endoprosthesis contain ePTFE, FEP, nitinol (nickel-titanium alloy), and gold.
- Patients with a systemic infection who may be at increased risk of endovascular graft infection.

### Literature review

van Sterkenburg et al. (2016) reported on a retrospective cohort analysis that analyzed procedural success and early outcome of endovascular treatment of a multicenter cohort of patients (n=46) with common iliac artery (CIA) aneurysms treated with the GORE EXCLUDER. The median diameter of the treated aneurysm was 40.5 (range, 25.0-90.0) mm and the mean procedural time was 198 ± 56 minutes. One implantation was not successful; two type 1b endoleaks were noticed, which resulted in procedural success rate of 93.5%. The two type 1b endoleaks spontaneously disappeared at 30 days and there was no 30-day mortality. Ipsilateral buttock claudication was present in two cases at 30 days and disappeared during follow-up. The incidence of reported erectile dysfunction was low and there was an absence of severe ischemic complications. After a mean follow-up of six months, data on 17 treated aneurysms were available: these showed two with a stable diameter, and 15 showed a mean decrease of 3.9 ± 2.2 mm (P<.001). Re-interventions were done in two patients (7.1%). The six-month primary patency of the internal component of the IBE device was 94%. The authors noted that prospective data with longer follow-up are awaited to establish the role of the device in the treatment algorithm of CIA aneurysms. Limitations of the study include small sample size and retrospective nature of the study.

### Use Outside of the US

CE Marking for this product was issued in 2013.

**European Society for Vascular Surgery:** this organization published clinical guidelines for the management of abdominal aortic aneurysms (Moll, et al., 2011). Recommendations regarding the management of iliac aneurysms include:

- Coexisting iliac aneurysms should be treated concurrently with AAA. Isolated iliac aneurysms may be treated by either open or, preferentially, endovascular techniques. Intervention should be considered when the iliac diameter exceeds 3 cm. Iliac aneurysms should be repaired once the diameter exceeds 3 cm.

Level 3a, Recommendation C

- Endovascular treatment options should be considered in all patients and in defined subgroups this will include the consideration for iliac branch graft placement.

Level 3a, Recommendation C

Level 3A: systematic review (with homogeneity) of case-control studies

Recommendation C: Level 4 studies or extrapolations from level 2 or 3 studies (Extrapolations are where data are used in a situation that has potentially clinically important differences than the original study situation).

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#### **Implanted Wireless Pulmonary Artery Sensor (e.g., CardioMEMS HF System) (HCPCS Codes C2624, C9741)**

Implantable intracardiac pressure monitors are intended to complement conventional drug therapy for heart failure (HF) through intermittent monitoring, allowing more timely adjustments to medications, if needed. The CardioMEMS™ HF System (St. Jude Medical, Inc., St. Paul, MN, USA, formerly Champion HF Monitoring System as well as Heart Sensor; CardioMEMS, Inc., Atlanta, GA) is a 2 x 3.4 x 15mm sized device that allows monitoring of pulmonary artery (PA) pressure using a wireless sensor. The sensor has two wire loops extending from either side. It is inserted into the PA through a traditional right heart catheterization procedure. Once deployed, PA pressure measurements can be taken repeatedly and transmitted wirelessly without requiring right heart catheterization or other invasive procedures. The sensor requires no batteries and is intended to be a permanent implant.

To record measurements at home, the patient lies on top of a pillow with sensory equipment embedded. A recording device with a cable-connected remote control is placed within four to five feet of the pillow. The patient reclines on the pillow and is guided to an optimal position by the recording device. When positioning is adequate, the machine prompts the patient to start recording by pushing the remote control. According to the manufacturer, the patient must remain still while pressures are recorded for 18 seconds, during which the machine plays music, intended to relax the patient. When the reading is complete, the machine automatically transmits the information to the CardioMEMS website (St. Jude Medical, 2014).

#### **U.S. Food and Drug Administration (FDA)**

Although a number of implantable wireless sensors are in development the CardioMEMS™ HF system is the only device in this group that has received FDA approval. On May 28, 2014 the Food and Drug Administration (FDA) granted CardioMEMS, Inc.'s (formerly Atlanta, GA, now St. Jude Medical, Inc., St. Paul, MN) premarket approval (PMA P100045) for the CardioMEMS HF System which includes the CM2000 implantable PA Sensor/Monitor and transvenous catheter delivery system, the CM1000 Patient Electronics System (GSM), the CM1010 Patient Electronics System (GSM), and CM3000 Hospital Electronics System. According to the PMA, the device is indicated for wirelessly measuring and monitoring pulmonary artery (PA) pressure and heart rate in patients with New York Heart Association (NYHA) Class III HF who have been hospitalized for HF in the previous year. The FDA approval requires that the manufacturer conduct an additional prospective, multi-center, open-label trial conducted in the United States to examine the safety and effectiveness of CardioMEMS HF System in 663 adults with NYHA Class III Heart Failure (HF) who have experienced a heart failure hospitalization within the



past 12 months; of which a total of 420 will be women. Follow-up will be two years post implant with specified safety and effectiveness endpoints. Additionally a prospective, multi-center, open-label substudy conducted in the United States to examine safety and compare the postmarket effectiveness of CardioMEMS HF System to premarket is required by the FDA.

### **Literature Review**

Data is limited in the published peer-reviewed scientific literature regarding the safety and effectiveness of the CardioMEMS HF System.

Hayes published a technology brief for wireless pulmonary artery pressure monitoring with CardioMEMS (CM) HF System for management of chronic heart failure (Hayes, 2016). The review included three clinical studies (n=12 to 550) that evaluated the accuracy, clinical utility, and safety of the CardioMEMS (CM) HF system for the management of patients with chronic heart failure. The system is a wireless implantable hemodynamic monitor (IHM) that measures pulmonary artery pressure (PAP) and heart rate in patients with heart failure (CM-IHM). Limitations of two poor-quality cohort studies included small numbers of patients, lack of data to calculate sensitivity, specificity, and predictive values, and use of echocardiography as a reference standard for diastolic PAP measurements. Although of good quality, the one randomized controlled trial was limited by a lack of data on any drug treatment modifications related to changes in patient management, and a lack of data on adverse events related to drug changes. It was found that overall, a low-quality body of evidence provides limited data suggesting that the CM-IHM system for patients with NYHA class III heart failure accurately monitors PAP, reduces heart failure-related hospitalizations through improved medical management over the first six months following implantation, and carries a minimal risk for serious adverse events.

Abraham et al. (2011) reported results of a randomized controlled trial (RCT): the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial. The outcomes of this trial were reviewed by the FDA for premarket approval of this device. Eligible patients underwent implantation of a wireless pulmonary artery (PA) sensor monitoring system (i.e., CardioMEMS). Five hundred fifty individuals were implanted and randomized to the treatment group (n=270, standard of care HF treatment, plus PA pressure readings) or to the control group (n=280, standard of care HF treatment). Daily PA pressure readings were taken at home by patients in each group and sent to a secure website. In the treatment group clinicians had access to these readings; in the control group clinicians were unable to access pressure readings. Assessment at one, three and six months, and every six-months thereafter included a physical examination, assessment of New York Heart Association class and quality-of-life assessment by use of the 21-question Minnesota Living with Heart Failure questionnaire and review of drugs.

The primary efficacy endpoint was the rate of heart failure-related hospitalizations during the six months after insertion of the pressure sensor in the treatment group versus the control group. The two primary safety endpoints were device-related or system-related complications. The mean follow-up was 15 months. At six months 83 heart-failure-related hospitalizations were reported in the treatment group compared with 120 in the control group ( $p<0.0001$ ). During the entire follow-up (mean 15 months) the treatment group had a 39% reduction in heart-failure-related hospitalization compared with the control group ( $p<0.0001$ ). Eight patients had device- or system-related complications (DSRC). Overall freedom from DSRC was 98.6%. Overall freedom from pressure-sensor failures was 100%. Survival rates in the treatment and control groups at six months were similar ( $p=0.45$ ). Fifteen serious adverse events (AE) were reported, including, infection, bleeding, thrombosis, cardiac arrhythmias, one patient with cardiogenic shock, one atypical chest pain, and one delivery-system failure that required a snare to remove the delivery system. Data in this single clinical trial suggest improved shortterm outcomes; however, additional large blinded RCTs replicating these findings are required before use of a wireless pulmonary artery sensor monitoring system (e.g., CardioMEMS HF system) is incorporated into routine clinical practice.

### **Use Outside of the US**

National Institute of Health Care and Excellence (NICE): NICE (2013) guidance on insertion and use of implantable pulmonary artery pressure monitors in chronic heart failure notes that current evidence on the safety and efficacy of the insertion and use of implantable pulmonary artery pressure monitors in chronic heart failure is limited in both quality and quantity. They recommend that this procedure should only be used with special arrangements for clinical governance, consent and audit or research.



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### **Intravascular Catheter-Based Coronary Vessel or Graft Spectroscopy (CPT Code 0205T)**

The leading cause of major morbidity and mortality is atherosclerotic cardiovascular disease, most commonly caused by thrombotic occlusion of a high-risk coronary plaque resulting in myocardial infarction or cardiac death, or embolization from a high-risk carotid plaque resulting in stroke (Alsheikh-Ali, 2010).

Near-infrared spectroscopy is proposed as a method to detect lipid and cholesterol deposits in coronary vessel walls. Ex vivo studies have demonstrated the feasibility of atherosclerotic lipid-rich plaque detection using near-infrared spectroscopy (NIRS). While near-infrared spectroscopy can collect data with rapid acquisition times, avoiding the need to obstruct blood flow it does not create an image of the vessel wall, which is a limitation of the device. Fibroatheromas that are thick capped or too small to be defined as lipid core plaques are major sources of false-positive readings (Alsheikh-Ali, 2010).

### **U.S. Food and Drug Administration (FDA)**

The LipiScan Coronary Imaging System (InfraReDx, Inc., Burlington, MA) received FDA 510(k) approval in April 2008. The device is indicated for the near-infrared examination of coronary arteries.

### **Literature Review**

Randomized controlled clinical trial data are lacking in the published peer-reviewed scientific literature. Waxman et al. (2009) reported initial results of the first-in-human uncontrolled validation study involving a catheter-based near-infrared spectroscopy system for the detection of lipid core coronary plaques (SPECTACL [SPECTroscopic Assessment of Coronary Lipid] trial). A total of 106 patients were enrolled in the study, spectroscopic data was obtained in 89 patients. Spectral similarity was demonstrated in 83% of available patients. The algorithm developed ex vivo identified the high-risk plaques in 60% of imaged segments in patients undergoing percutaneous coronary intervention. The authors note the feasibility of invasive detection of coronary lipid core plaques with this system.

### **Professional Societies/Organizations**



Guidelines from the American Heart Association and the American College of Cardiology do not include guidance regarding use of intravascular catheter-based coronary vessel or graft spectroscopy to identify lipid core plaques or for any indication.

#### **Use Outside of the US**

No relevant information.

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#### **Acoustic Cardiography (CPT code 93799)**

Acoustic cardiography, also referred to as correlated audioelectric cardiography is a noninvasive diagnostic tool designed to be used in the evaluation of cardiac conditions such as left ventricular hypertrophy (LVH), acute and age-undetermined myocardial infarction (MI), cardiac arrhythmias, and detection of S3 and S4 heart sounds. An S3 heart sound may be associated with heart failure in patients over age 40. Acoustic cardiography is intended to augment physician auscultation, since S3 and S4 heart sounds may be difficult to hear in some patients. The device acquires, displays, and analyzes 12-lead electrocardiogram (ECG) and heart sound data (Collins et al., 2006; Kobza et al., 2008; Wagner et al., 2002; Warner et al., 2002).

Traditional diagnostic methods include physical examination and auscultation, 12-lead ECG laboratory examinations, measurement of biomarkers of cardiac damage, and imaging.

#### **U.S. Food and Drug Administration (FDA)**

The Eli 200+ Audicor (Mortara Instrument, Inc., Milwaukee, WI) is an interpretive electrocardiograph device designed to acquire, record and store cardiac data. The device uses Audicor Correlated Audioelectric Cardiography (COR) technology (Inovise Medical, Inc., Newberg, OR) to simultaneously acquire both 12-lead electrocardiogram (ECG) and heart sound data. The Eli 200+ Audicor received U.S. Food and Drug Administration (FDA) clearance to market as a Class II device through the 510(k) process on July 25, 2003. The device was considered a technology evolution and substantially equivalent to the ELI 200, Inovise's Cardiovisc Interpretive Software, and Hewlett Packard's 1514A ECG/Phono System.

The FDA 510(k) notification of clearance to market the Eli 200+ Audicor included the following indications for use:

- The device is indicated for use to acquire, analyze, display and print ECG and heart sound data (COR).
- The device is indicated for use to provide interpretation of the data for consideration by physicians.
- The device is indicated for use in a clinical setting by a physician or by trained personnel and is not intended as a sole means of diagnosis.
- The interpretations of ECG and heart sound data (COR) offered by the device are only significant when used in conjunction with physician over-read as well as consideration of all other relevant patient data.
- The device is intended for use on adult populations, typically symptomatic.
- The device is not intended to be used as a vital signs physiological monitor.



- The device is indicated for evaluation of cardiac conditions such as left ventricular hypertrophy (LVH), acute and age-undetermined myocardial infarction (MI), and detection of S3 and S4 heart sounds.

On October 31, 2003, the Audicor Upgrade System received FDA clearance as a Class II device through the 510(k) process. The Audicor Upgrade System is an add-on device used with Audicor Sensors in the V3 and V4 positions on the chest wall. The system consists of a pocket personal computer (PC) with proprietary software and can be used with several models of existing electrocardiographs to allow physicians access to the COR report, including graphical display of MI and LVH conditions, display of heart sound waveforms, and identification of S3 and S4 heart sounds.

The Zargis Acoustic Cardioscan (Zargis Medical Corporation, Princeton, NJ) received FDA approval through the 510(k) process on May 26, 2004. The system is an electronic auscultatory device intended to acquire, record, and analyze heart sounds. The system consists of an electronic stethoscope, notebook computer, software, printer and an isolation transformer. According to the FDA indications for use, the device acquires and records the acoustic signals of the heart and analyses these signals. The analysis procedure will identify specific heart sounds that may be present, including S1, S2, and suspected murmurs. The approval lists the Audicor system as a predicate device.

### Literature Review

Published studies have evaluated the use of Cardiovisc diagnostic software, a predicate device and component of the Audicor System, for the detection of acute and prior MI (Wagner, et al., 2002; Andresen, et al., 2002). Published studies involving the Audicor system or correlated audioelectric cardiography are limited.

Wang reported on results of a prospective cohort study of 474 patients with heart failure (HF) to evaluate whether acoustic cardiography can identify HF patients at high risk for mortality. Acoustic cardiographic parameters included S3 score and systolic dysfunction index (SDI) (correlated closely with left ventricular systolic dysfunction). The event-free survival curves were plotted by Kaplan-Meier method and Cox regression analysis was used to identify independent predictors for all-cause mortality. With a mean follow-up of 484 days, 169 (35.7%) patients died and 126 (26.6%) were due to cardiac causes. After controlling for age, systolic blood pressure, hemoglobin, blood urea nitrogen, albumin, as well as ACEI and beta-blocker treatment in multivariate Cox regression analysis, SDI  $\geq 5$  and S3 score  $\geq 4$  were both independent predictors for all-cause mortality. Kaplan-Meier analysis showed that HF patients with SDI  $\geq 5$  or S3 score  $\geq 4$  had a significantly lower survival (52.2% vs. 69.2%, Log-rank  $\chi^2=18.07$ ,  $P<0.001$ ; 56.8% vs. 68.6%, Log-rank  $\chi^2=10.58$ ,  $P=0.001$ , respectively) than those with lower SDI or S3 score. The study was limited by the lack of randomization. Limitations noted in the study included that adverse nonfatal outcomes including rehospitalization or severe medical complications were not evaluated in this study and further investigations focusing on prediction of subsequent cardiovascular events are warranted; BNP was not routinely measured in heart failure patients and not included as biomarker in the analysis; and, heart failure patients with atrial fibrillation were not excluded from our study.

Wang et al. (2013) reported the results of a prospective cohort study ( $n=272$ ) to determine the diagnostic utility of acoustic cardiography in patients with heart failure (HF). Cohort subjects had hypertension ( $n=94$ ), heart failure (HF) and normal ejection fraction (HRNEF,  $n=109$ , EF $\geq 50\%$ ) and HF and reduced EF (HRREF,  $n=89$ , EF $<50\%$ ). All participants received acoustic cardiography and echocardiography examinations. Acoustic cardiographic parameters included S3 score, electromechanical activation time (EMAT) and systolic dysfunction index (SDI). EMAT significantly differentiated HFNEF from hypertension (area under curve [AUC], 0.83; 95% confidence interval [CI], 0.77–0.89) with a sensitivity and specificity of 55% and 90%, respectively. An echocardiogram yield a sensitivity of 55% and 90% specificity. An SDI $>5.43$  yielded 53% sensitivity and 91% specificity. The authors note that this technology may be helpful in identifying HF and its phenotypes when echocardiography is not available. The study is limited by small size, uncontrolled design and low sensitivity and specificity results.

Collins et al. (2009) conducted a multisite study to evaluate the effect of an S3 captured by acoustic cardiography on diagnostic accuracy and confidence in the diagnosis of acute decompensated heart failure in patients presenting to the emergency department (ED) with dyspnea ( $n=995$ ). The study also evaluated the impact on patient prognosis. ED physicians who were initially blinded to all laboratory and acoustic cardiography results estimated the probability of acute decompensated heart failure on a scale of 0% to 100% on a visual analog scale. The visual analog scale was repeated after acoustic cardiography results were provided. Patients



were followed for 90 days to determine the relationship of the S3 to adverse events. The initial sensitivity, specificity, and accuracy for acute decompensated heart failure as a possible diagnosis were 89.0%, 58.2%, and 71.0%, respectively. Sensitivity, specificity, and accuracy for acoustic cardiography were 40.2%, 88.5%, and 68%, respectively. The authors concluded that acoustic cardiography S3 was specific to acute decompensated heart failure, but did not improve diagnostic accuracy, primarily because of the low sensitivity. In addition, the acoustic cardiography S3 provided no significant independent prognostic information.

Maisel et al. (2011) conducted a secondary analysis of the Collins study (2009) to determine if the strength of the S<sub>3</sub> can provide diagnostic prognostic information in problematic heart failure subgroups. The analysis included dyspneic ED patients older than age 40 who were not on dialysis. A gold standard acute heart failure diagnosis was determined by two cardiologists who were blinded to acoustic cardiography results. In the 995 enrolled patients, S<sub>3</sub> strength was a significant prognosticator in univariate analysis for adverse events. When results were incorporated into the multivariable analysis in stepwise fashion, however, it was not as predictive as other variables, such as B-type natriuretic peptide (BNP) values and ST-depression on ECG. In the subgroup of patients with "gray zone" BNP levels, acoustic cardiography increased diagnostic accuracy of acute heart failure (AHF) from 47% to 69%. Acoustic cardiography also improved S<sub>3</sub> detection sensitivity in obese patients compared to auscultation. The authors stated that although acoustic cardiography appears to augment the use of BNP, particularly in problematic subgroups, there were limitations to the study, including the fact that the true diagnostic characteristics when used in real time are unknown, due to the retrospective nature of the study and limited data availability. In addition, cardiologists making the AHF diagnosis were not blinded to BNP results, which would have impacted the diagnosis.

Kobza et al. (2008) conducted a case series (n=57), to evaluate the use of acoustic cardiography using the Audicor device) during electrophysiological (EP) testing for known or suspected cardiac arrhythmias concluding that acoustic cardiography is useful for identifying VT and may facilitate the differential diagnosis of clinically important tachyarrhythmias, particularly when advanced techniques such as EP studies are not available.

Collins et al. (2006) evaluated the use of an S3 heart sound combined with B-type natriuretic peptide (BNP) levels in the diagnosis of emergency room patients with dyspnea (n=439). The author concluded that an S3 sound is highly specific for heart failure and is ideally suited for use in combination with BNP to improve diagnostic accuracy. The sensitivity, specificity, positive and negative predictive value, and diagnostic accuracy of the electronic S3 for primary heart failure were 34%, 93%, 66%, 7%, and 70%, respectively. The values obtained by physician auscultation were 16%, 97%, 84%, 3%, and 66%, respectively. The addition of an Audicor S3 to intermediate BNP levels improved the positive likelihood ratio from 1.3 to 2.9 and improved the positive predictive value from 53% to 80%. The overall ER misdiagnosis rate was 14%. Of the 48 cases, 44 were a failure to diagnose heart failure when it was present. If the Audicor had been used as the sole diagnostic tool among these 44 ultimately considered to have primary HF, 15 would have been correctly diagnosed. Similarly, if the Audicor tool had been used as the sole diagnostic tool, 14 of the 206 patients correctly diagnosed as nonprimary HF would have been incorrectly diagnosed as primary HF. Although the evaluation of S3 heart sounds in combination with BNP testing may improve diagnostic accuracy in patients with dyspnea of unclear etiology, this study does not demonstrate that the Audicor system provides a benefit, when used alone or in combination with other tests, in terms of improved clinical outcomes.

Marcus et al. (2006) conducted a prospective study to determine the diagnostic test characteristics of the S3 and S4 heart sounds for prediction of left ventricular dysfunction using the Audicor system in patients undergoing elective left-sided heart catheterization (n=90). Patients underwent computerized heart sound phonocardiographic analysis (Audicor system) for assessment of S3/S4 heart sounds, cardiac catheterization for assessment of left ventricular end-diastolic pressure (LVEDP), transthoracic echocardiography for evaluation of left ventricular ejection fraction (LVEF), and blood sampling for BNP. Mean LVEDP was significantly elevated; LVEF was reduced; and median BNP was elevated in those with an S3, S4, or both, compared to patients without a diastolic heart sound. The sensitivities of these heart sounds to detect an elevated LVEDP, reduced LVEF, or elevated BNP were 41%, 52%, 32% for an S3, and 46%, 43%, and 40% for an S4, respectively. The authors concluded that neither the phonocardiographic S3 nor the S4 is a sensitive marker of left ventricular dysfunction. The absence of an S3 or S4 using phonocardiographic testing (Audicor system) is therefore not sufficient to exclude ventricular dysfunction. If present, the phonocardiographic S3 and S4 are specific for an elevated LVEDP, depressed LVEF, and elevated BNP level.



## Professional Societies/Organizations

**American College of Cardiology/American Heart Association (ACC/AHA):** ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction (O'Gara, et al., 2013) and the ACC/AHA Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (Yancey, et al., 2013), do not include the use correlated audioelectric cardiography or acoustic heart sounds as a diagnostic tool. In addition, this technology is not mentioned in AHA/ACC Recommendations for the Standardization and Interpretation of the Electrocardiogram, Part I (Kligfield, et al., 2007) and II (Mason, et al., 2007).

**American Heart Association (AHA):** The AHA scientific statement, Acute Heart Failure Syndromes: Emergency Department Presentation, Treatment, and Disposition: Current Approaches and Future Aims, includes a discussion of focused areas for future investigation. The authors note that the search for additional tools to improve the diagnostic accuracy for patients with undifferentiated dyspnea and possible acute heart failure syndromes remains a high priority. Electronic detection of third heart sounds (S<sub>3</sub>) using acoustic cardiography is included among several tools that have been investigated as both stand-alone and adjunct diagnostic measures, but appear to provide little benefit over existing approaches (Weintraub et al., 2010).

## Use Outside of the US

**Australian and New Zealand Horizon Scanning Network ([ANZHSN], 2010):** A Horizon Scanning Technology Prioritizing Summary notes that although comparative evidence indicated that the adjunctive use of acoustic cardiography may be of benefit in the diagnosis of heart failure, the application of this technology in the acute setting was considered impractical.

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#### **Transluminal Peripheral Atherectomy (CPT Codes 0234T, 0235T, 0236T, 0237T, 0238T)**

Peripheral artery disease (PAD) broadly encompasses the vascular diseases caused primarily by atherosclerosis and thromboembolic pathophysiologic processes that alter the normal structure and function of the aorta, its visceral arterial branches, and the arteries of the lower extremity (American College of Cardiology Foundation [ACCF]/American Heart Association [AHA], 2011). PAD may be treated medically, and with angioplasty and stenting for patients not responding to medical treatment. Atherectomy involves the removal of plaque burden using physical or ablative means (e.g., laser) in a directional (proximal to distal, usually) or rotational manner and may or may not be combined with angioplasty and stenting (Zaetta, et al. 2017). Atherectomy may be used in the atherectomy of femoral, popliteal artery and tibial, peroneal artery. It has been proposed to be used in the treatment of in arteries above the inguinal ligaments (renal, visceral, abdominal aorta, brachiocephalic trunk and branches and iliac artery).

#### **Literature Review**

The medical literature has shown atherectomy to be both safe and effective in femoro-popliteal and infrapopliteal segments. The published peer reviewed scientific literature is preliminary and limited for atherectomy in arteries above the inguinal ligaments (renal, visceral, abdominal aorta, brachiocephalic trunk and branches and iliac artery) and mainly involves small retrospective studies of procedures involving iliac artery.

Valle et al. (2017) reported on a case study of orbital atherectomy in the renal vasculature. A retrospective, uncontrolled, single-center study (Thatipelli, et al., 2009) evaluated the safety and efficacy of blunt microdissection in patients with symptomatic CTOs of the pelvis and lower extremities. Follow-up data were available for up to 1 year. The study included 61 patients who underwent 67 procedures in 86 arteries. The target lesion was located in the aortoiliac artery in 11 of 87 segments (13%), femoropopliteal artery in 72 (83%), and infrapopliteal artery in 4 (5%). All had severe claudication, rest pain, or tissue loss. The authors concluded that this treatment is safe and efficacious, but also noted that the results, drawn from a group of patients referred



to a tertiary center, may not be applicable to the general population of patients with PAD. Furthermore, the follow-up data are incomplete since a high number of cases were not included, which limits the ability to determine the actual rates of treatment success.

### **Professional Societies/Organizations**

**American College of Cardiology Foundation/American Heart Association ([ACCF/AHA], 2011):** The ACCF/AHA published a guideline titled, Management of Patients with Peripheral Artery Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic), which is adapted from the 2005 ACCF/AHA Guideline and the 2011 ACCF/AHA focused update. Regarding endovascular treatment of claudication the Guideline notes:

- Class IIa, Level of Evidence C recommendation notes that stents (and other adjunctive techniques such as lasers, cutting balloons, atherectomy devices, and thermal devices) can be useful in the femoral, popliteal, and tibial arteries as salvage therapy for a suboptimal or failed result from balloon dilation (e.g., persistent translesional gradient, residual diameter stenosis >50%, or flow limiting dissection).
- Class IIb, Level of Evidence A recommendation notes that the effectiveness of stents, atherectomy, cutting balloons, thermal devices, and lasers for the treatment of femoral-popliteal arterial lesions (except to salvage a suboptimal result from balloon dilation) is not well established.
- Class IIb, level of evidence C recommendation notes that the effectiveness of uncoated/uncovered stents, atherectomy, cutting balloons, thermal devices, and lasers for the treatment of infrapopliteal lesions (except to salvage a suboptimal result from balloon dilation) is not well established."

Definitions regarding class and level of evidence ratings are as follows:

Class IIa, Level of Evidence: A: Benefit >>Risk. Additional studies with focused objectives needed. It is reasonable to perform procedure/administer treatment, recommendation in favor of treatment or procedure being useful/effective, some conflicting evidence from multiple randomized trials or meta-analyses;

Class IIb, Level of Evidence: A: Benefit ≥ Risk. Additional studies with broad objectives needed; additional registry data would be helpful. Procedure/Treatment may be considered. Recommendation's usefulness/efficacy less well established, greater conflicting evidence from multiple randomized trials or meta-analyses;

Class IIb, Level of Evidence: C: Benefit ≥ Risk. Additional studies with broad objectives needed; additional registry data would be helpful. Procedure/Treatment may be considered. Recommendation's usefulness/efficacy less well established. Only diverging expert opinion, case studies, or standard of care.

### **Use Outside of the US**

**European Stroke Organisation/European Society of Cardiology (ESC):** In a practice guideline on the diagnosis and treatment of peripheral artery diseases, these organizations states that atherectomy devices have unclear long-term benefits and that aortoiliac or bifemoral bypass is usually recommended for diffuse aortoiliac disease. Owing to the limited probability of improvement in symptoms with exercise therapy in the case of aortoiliac lesions, revascularization should be considered without initial conservative treatment. Surgery is limited to extensive lesions without the possibility for endovascular treatment. In patients with disabling intermittent claudication that impacts their activities of daily living, with culprit lesions located at the aorta/iliac arteries, revascularization (endovascular or surgical) should be considered as the first choice therapeutic option. In the external iliac arteries, a primary stenting strategy using self-expandable stents is preferred over provisional stenting, mainly due to a lower risk of dissection and elastic recoil (European Stroke Organisation/ESC 2011).

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#### **Near-Infrared Guidance for Vascular Access Requiring Real-Time Digital Visualization for Evaluation of Potential Access Sites and Vessel Patency (CPT Code 99199)**

A peripheral venous catheter is most commonly used for venous access. Traditional techniques for determining the location of a peripheral vein includes palpating the skin, and unaided visualization of the skin in ambient light (Perry, 2011). Use of a near-infrared imaging system has been proposed as an alternative method to aid in visualization of the superficial vasculature. The imaging system provides a display of peripheral vasculature in real-time. It is purported to reduce the number of intravenous (IV) attempts, reduce the time it takes to initiate an IV and improve patient satisfaction (Christie Medical, 2013).

**U.S. Food and Drug Administration (FDA):** The VTS1000 Liquid Crystal Vein Locator (VueTek Scientific™, LLC, Gray, MN) received 510 (k) approval on Feb 18, 2011. The VTS1000 is a noninvasive electronic device to aid in the visualization of superficial vasculature. According to the 510(k) summary it is indicated for use during procedures requiring vascular or peripheral vascular access.

#### **Literature Review**

Rothbart et al. (2015) reported on a retrospective study of that examined the use of Accuvein® AV300 vein viewer used to facilitate venous cannulation in children. The study included 238 consecutive pediatric patients preceding surgical interventions. The subjects were allocated to groups [control group (124 patients) and intervention group (114 patients)] in a non-random way - randomization was not feasible because data was acquired retrospectively. In control group, peripheral IV cannulation was performed without supporting device, in intervention group with support of AV300. Time and number of attempts until successful venous cannulation were defined as primary end points. The study found that the median time until successful cannulation was 2 min (range 0.1-20, quartiles: 25%: 1; 75%: 5) in the intervention group and 1 min (range 0.1-18, quartiles: 25%: 0.2; 75%: 2) in the control group ( $p < 0.01$ ). Median number of attempts was higher in the intervention group (2; range 1-6, quartiles: 25%: 1; 75%: 3) than in the control group (1; range 1-6, quartiles: 25%: 1; 75%: 2,  $p < 0.01$ ). the rate of cannulations successful at first attempt was 0.45 (51 of 114, 95% CI 0.35-0.54) in the intervention group and 0.73 (90 of 124, 95% CI 0.65-0.81) in the control group ( $p < 0.01$ ). the authors concluded that they were not able to reduce neither time nor number of attempts until a successful venous cannulation in children using the vein viewer and that laser-supported cannulation cannot be recommended for standard procedures. The study was limited with the lack of randomization.

Van der Woude et al. (2013) reported results of a pragmatic cluster randomized controlled clinical trial using the VascuLuminator in a population of children with dark skin color requiring intravenous (IV) cannulation in the operating room. Eighty-eight patients were included in the study (control, n=45; VascuLuminator, n=43). The



availability of the VascuLuminator to anesthesiologists at the operating complex was randomized by computer in clusters of one week. In the VascuLuminator group IV cannulation was aided by the device, whereas the device was not available at the operating room in the control group. Success at first attempt was not significant between the two groups ( $p=0.27$ ). Median time to successful cannulation was not significant between groups ( $p=.54$ ). In the subgroup of children a priori anticipated to be difficult to cannulate (i.e., "hard" or "very hard"), there was a trend to higher success at first attempt in the VascuLuminator group ( $p = 0.03$ ). The authors noted data suggest limited value of the VascuLuminator in facilitating IV cannulation in a subgroup of children with dark skin color who are anticipated to be difficult to cannulate.

Kim et al. (2012) evaluated a group of 111 children who were randomized into one of the two groups (VeinViewer,  $n=54$ ) or control ( $n=57$ ). There was no significant difference in the overall first attempt success rate using the VeinViewer compared with control ( $p=0.526$ ). There was no significant difference between the groups for easy ( $p=0.485$ ), or difficult patients ( $p=.0026$ ). Limitations to the study cited by the authors included that the procedural time was analyzed only in patients with successful venous access on the first attempt because the time interval after the first failed attempt varied according to the operator and the situation. Further, the amount of training and practice to attain proficiency with the VeinViewer has not been established.

Phipps et al. (2012) randomized 115 preterm and term neonates undergoing placement of peripherally inserted central catheters by use of VeinViewer ( $n=59$ ) or standard techniques ( $n=56$ ). Overall, there was a trend to more successful placement using VeinViewer, but no statistical significance ( $p=0.08$ ). When analysis was limited to the first attempt at cannulation no differences between the two techniques were found ( $p=0.55$ ). Additionally, infants randomized to the VeinViewer were more mature ( $30\pm 2$  weeks gestational age (GA) versus  $28\pm 2$  weeks GA;  $p=0.08$ ). Study limitations included lack of blinding regarding use of VeinViewer compared with standard techniques. Larger studies are needed to demonstrate the effectiveness of this device over standard techniques for attaining peripheral venous access.

Chapman et al. (2011) reported results of a prospective, randomized study of children aged 0 to 17 who required nonemergent peripheral intravenous (PIV) catheter placement. Participants were randomized to standard PIV cannulation or PIV cannulation with the VeinViewer (Christie Medical Holdings, Cypress, CA, formerly Luminetx, Memphis, TN). The primary outcome measure was time to PIV placement. Secondary outcome measures included number of PIV attempts and pain scores as reported by the child, parent or guardian and nurse. A total of 323 patients completed the study. No differences in time to PIV placement, number of PIV attempts or pain scores was noted for the overall study group. However, a planned subgroup analysis of children aged 0 to 2 ( $n=107$ ) did yield significant results for time to PIV placement ( $p<0.047$ ), and for nurses' perception of pain ( $p=0.01$ ). Data did not support improvement in outcomes for the total study group. Additional randomized controlled trials (RCT) should be conducted to determine the role of this device for evaluation of potential access sites.

Perry et al. (2011) conducted a prospective RCT to determine whether the use of a near-infrared light venipuncture aid (VeinViewer, Christie Medical Holdings, Cypress, CA, formerly Luminetx, Memphis, TN) would improve the rate of successful first-attempt placement of intravenous (IV) catheters in a high-volume pediatric emergency department (ED). One hundred twenty-three patients were randomized to use of the device ( $n=62$ ) or the traditional technique of palpation of the overlying skin and unaided visualization of peripheral veins for IV access using only ambient room light ( $n=61$ ). If a vein could not be cannulated after three attempts, patients crossed over from one study arm to the other, and study nurses attempted placement with the alternative technique. The primary end point was first-attempt success rate for intravenous (IV) catheter placement. After completion of patient enrollment, a questionnaire was completed by study nurses as a qualitative assessment of the device. There was no significant difference in first-attempt success rate between the standard and device groups. Of the 19 study nurses, 14 completed the questionnaire. Seventy percent expressed neutral or unfavorable assessments of the device in nondehydrated patients. Ninety percent of nurses found the device a helpful tool for patients in whom IV access was difficult. Additional RCTs with large patient populations should be conducted to demonstrate the role of the device in these patients.

#### **Use Outside of the US**

No relevant information.



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## **Intravascular Optical Coherence Tomography (OCT) (Coronary Native Vessel or Graft) (CPT Codes 92978, 92979)**

Invasive coronary angiography is considered the gold standard for evaluating patients with suspected myocardial ischemia. Intracoronary optical coherence tomography (OCT) is an intravascular imaging technique performed during cardiac catheterization that measures the echo time delay and intensity of backscattered light from tissue's internal microstructure. This diagnostic procedure creates high-resolution, cross-sectional images of the coronary arteries to permit quantification of lumen dimensions and the extent of lumen narrowing, visualization of atherosclerotic plaque, and characterization of the structure and extent of plaque.

OCT systems comprise a fiberoptic imaging catheter attached to a patient interface unit, which connects to a system console. The console contains an optical engine (i.e., light source, beam splitter, reference arm, detectors, signal processor) and a computer that collects multiple light signals reflected from different tissue depths and combines them to make a three-dimensional image. Signal intensity is mapped to a color space that is displayed on a monitor.

OCT is frequently compared to intravascular ultrasound (IVUS). Compared to IVUS, it is purported that OCT provides enhanced contrast between lumen and vessel walls, higher axial resolution of intracoronary plaque structures, and faster pullback. OCT catheters are smaller in diameter than IVUS catheters, allowing safer image acquisition from smaller-caliber vessels (St. Jude Medical, 2012).

The major limitation of OCT is its inability to consistently image the outer layer of the vessel wall and assess plaque burden due to limited tissue penetration (1.0 to 1.5 mm). Also, using OCT to measure large-diameter vessels at proximal target sites may be difficult, and the manufacturer has indicated that aorto-ostial lesions are not suitable for OCT imaging.

**U.S. Food and Drug Administration (FDA):** Several intracoronary optical coherence tomography products made by St. Jude Medical, Inc., (St. Paul, MN), have received FDA 510 (k) approval. These include the C7 XR Imaging system (April 2010) and the C7 Dragonfly Intravascular Imaging catheter and disposable accessories (April, 2010). Others include the ILUMIEN System, (LightLab Imaging, Inc., Westford, MA, July 2011) and the OCT Imaging system and catheter (Volcano Corporation (San Diego, CA) received 510(k) approval on Jan, 2010).

## Literature Review

Although there are a number of prospective and retrospective studies and review articles in the published peer-reviewed scientific literature, randomized controlled trial data are lacking to inform health outcomes as a result of intracoronary optical coherence tomography. A number of clinical trials are ongoing.



Ali et al (2016) reported on a randomized controlled trial that examined whether or not a novel OCT-based stent sizing strategy would result in a minimum stent area similar to or better than that achieved with IVUS guidance and better than that achieved with angiography guidance alone. The primary efficacy endpoint was post-PCI minimum stent area, measured by OCT at a masked independent core laboratory at completion of enrolment, in all randomly allocated participants who had primary outcome data. The primary safety endpoint was procedural major adverse cardiovascular events (MACE). The study randomly allocated 450 patients (158 [35%] to OCT, 146 [32%] to IVUS, and 146 [32%] to angiography), with 415 final OCT acquisitions analyzed for the primary endpoint (140 [34%] in the OCT group, 135 [33%] in the IVUS group, and 140 [34%] in the angiography group). The final median minimum stent area was 5.79 mm<sup>2</sup> (IQR 4.54-7.34) with OCT guidance, 5.89 mm<sup>2</sup> (4.67-7.80) with IVUS guidance, and 5.49 mm<sup>2</sup> (4.39-6.59) with angiography guidance. OCT guidance was non-inferior to IVUS guidance (one-sided 97.5% lower CI -0.70 mm<sup>2</sup>; p=0.001), but not superior (p=0.42). OCT guidance was also not superior to angiography guidance (p=0.12). Procedural MACE was noted in four (3%) of 158 patients in the OCT group, one (1%) of 146 in the IVUS group, and one (1%) of 146 in the angiography group (OCT vs IVUS p=0.37; OCT vs angiography p=0.37). The authors concluded that OCT using a specific reference segment external elastic lamina-based stent optimization strategy was safe and resulted in similar minimum stent area to that of IVUS-guided PCI, however the results warrants a large-scale randomized trial to establish whether or not OCT guidance results in superior clinical outcomes to angiography guidance.

Meneveau et al. (2016) reported on a multicenter, randomized study involving 240 patients with non-ST-segment elevation acute coronary syndromes to compare OCT-guided PCI (use of OCT pre- and post-PCI; OCT-guided group) to fluoroscopy-guided PCI (angiography-guided group). The primary end point was the functional result of PCI assessed by the measure of post PCI fractional flow reserve. The secondary end points included procedural complications and type 4a peri-procedural myocardial infarction and safety was assessed by the rate of acute kidney injury. Findings included that OCT use led to a change in procedural strategy in 50% of the patients in the OCT-guided group. The primary end point was improved in the OCT-guided group, with a significantly higher fractional flow reserve value (0.94±0.04 versus 0.92±0.05, P=0.005) compared with the angiography-guided group. There was no significant difference in the rate of type 4a myocardial infarction (33% in the OCT-group versus 40% in the angiography-guided group, P=0.28). The rates of procedural complications (5.8%) and acute kidney injury (1.6%) were identical in each group despite longer procedure time and use of more contrast medium in the OCT-guided group. Post-PCI OCT revealed stent under-expansion in 42% of patients, stent malapposition in 32%, incomplete lesion coverage in 20%, and edge dissection in 37.5%. This led to the more frequent use of post-stent overdilation in the OCT-guided group versus the angiography-guided group (43% versus 12.5%, P<0.0001) with lower residual stenosis (7.0±4.3% versus 8.7±6.3%, P=0.01). The authors concluded that in patients with non-ST-segment elevation acute coronary syndromes, OCT-guided PCI is associated with higher post-procedure fractional flow reserve than PCI guided by angiography alone. The procedure did result in longer procedure time, but did not increase peri-procedural complications, type 4a myocardial infarction, or acute kidney injury.

Hayes published a directory report for optical coherence tomography (OCT) for plaque characterization and stent implantation (Hayes, 2016). The review included 19 studies, including 8 prospective and 5 retrospective uncontrolled or noncomparative cohort studies; one retrospective comparative cohort study; one prospective, case-matched cohort study; two retrospective, case-matched cohort or cross-sectional studies; and two randomized controlled trials (RCTs). The review noted that reviewed studies provide consistent evidence that OCT can detect features of plaques and stents that are associated with increased risk of adverse cardiac events. However, the reviewed studies do not provide sufficient evidence to conclude that the information obtained with OCT can be used to improve patient management and reduce the risk associated with adverse plaque and stent characteristics, particularly relative to guidance of percutaneous coronary interventions (PCI) with intravascular ultrasonography (IVUS). Additional well-designed studies are needed to determine whether guidance of PCI with OCT and angiography improves patient outcomes versus guidance with IVUS and angiography or with angiography alone.

#### **Professional Societies/Organizations**

##### **American College of Cardiology Foundation, American Heart Association, and Society for**

**Cardiovascular Angiography and Interventions Association Task Force:** These Societies published a joint practice guideline titled, Percutaneous Coronary Intervention (Levine, et al., 2011). The guideline notes that



compared with IVUS, optical coherence tomography has greater resolution (10 to 20 micronmeter axially) but more limited depth of imaging (1 to 1.5 mm). Unlike IVUS, optical coherence tomography requires that the artery be perfused with saline solution or crystalloid during image acquisition and therefore does not permit imaging of ostial lesions. Clinical studies have shown low optical coherence tomography complication rates, similar to those of IVUS. The excellent resolution of optical coherence tomography permits detailed in vivo 2-dimensional imaging of plaque morphological characteristics (e.g., calcification, lipid, thrombus, fibrous cap thickness, and plaque ulceration or rupture) and evaluation of the arterial response to stent implantation (e.g., stent strut neointimal thickness and apposition) and may be of value in clinical research. The practice guideline notes the appropriate role for optical coherence tomography in routine clinical decision making has not been established.

### **Use Outside of the US**

**The Task Force on Myocardial Revascularization of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery:** These Societies published joint Guidelines on Myocardial Revascularization in 2010. These guidelines note that OCT is a light-based modality of intravascular imaging with higher spatial resolution than intravascular ultrasound (15µm vs. 100µm). Its penetration is lower than intravascular ultrasound but it provides detailed imaging of the endoluminal borders. At present, OCT is a valuable research tool.

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### **Endothelial Function Assessment (CPT Code 0337T)**

The endothelium helps to regulate vascular tone, cellular adhesion, thromboresistance, smooth muscle cell proliferation, and vessel wall inflammation. Alteration in endothelial function precedes the development of morphological atherosclerotic changes and can also contribute to lesion development and later clinical complications (Deanfield, 2007). Noninvasive endothelial function assessment has been proposed as a means to predict the risk of atherosclerosis and cardiovascular disease.

One method involves measurement of the brachial diameter before and after an increase in shear stress induced by reactive hyperemia or flow-mediated dilation (FMD). Special probes that have pneumoelectrical tubing that connect to a computer are placed in an arm stabilizer and the index finger is placed in a probe. A



sphygmomanometer cuff is placed on the forearm distal to the brachial artery, inflated and released for a timed period. This is repeated with higher pressures used to mimic occlusion. Finally the pressures are measured five minutes after the pressure is released. FMD occurs as a result of local endothelial release of nitrous oxide. The information is evaluated by proprietary software and a score indicating the endothelial health is generated. Digital peripheral arterial tonometry (PAT) quantifies reactive hyperemia-induced changes in pulse volume amplitude (PVA) in the finger tip, and is an automated method to non-invasively assess endothelial function (Lee, 2012). According to the manufacturer, EndoPAT™ measures several vascular beds, composed of small vessels and microcirculation. The manufacturer also notes the EndoPAT™ corrects for systemic changes by a simultaneous measurement from the (un-occluded) contra-lateral arm.

**U.S. Food and Drug Administration (FDA):** The Endo PAT 2000 device (Itamar Medical, Inc., Framingham, MA) received 510(k) approval in November 2003. According to the approval summary it is a non-invasive device, intended for use as a diagnostic aid in the detection of coronary artery endothelial dysfunction (positive or negative) using a reactive hyperemia procedure. The summary also notes “The Endo PAT 2000 has been shown to be predictive of coronary artery endothelial dysfunction in the following patient population: patients with signs or symptoms of ischemic heart disease, who are indicated for coronary artery angiography, but who lack angiographic evidence of obstructive coronary artery disease. The device is intended to be used in a hospital or clinic environment by competent health professionals. The Endo PAT 2000 device is not intended for use as a screening test in the general patient population. It is intended to supplement, not substitute, the physician’s decision-making process. It should be used in conjunction with knowledge of the patient’s history and other clinical findings.”

The CVProfilor® System, Cardiovascular Profiling System, original applicant Hypertension Diagnostics, Inc. (Eagan, MN) received 510(k) approval (K001948) from the FDA in November, 2000 as a Class II device for the noninvasive measurement of blood pressure and pulse rate. According to the summary “It is classified as a noninvasive blood pressure measurement system providing a signal from which systolic, diastolic, mean, or any combination of the three pressures can be derived through the use of transducers placed on the surface of the body.”

### Literature Review

Randomized controlled clinical trial data are lacking to demonstrate the clinical utility and effectiveness of endothelial function assessment to predict cardiovascular risk. The majority of studies in the published peer-reviewed literature are prospective cohorts.

Hayes published a technology directory report on peripheral arterial tonometry (PAT), a noninvasive device intended for the evaluation of endothelial dysfunction using indirect measurement of induced reactive hyperemia (RH) (Hayes, 2014; 2015; 2016). The review included ten peer-reviewed cross-sectional or prospective cohort studies evaluating RH-PAT, with sample size of 60 to 238 patients. Six studies investigated RH-PAT for: detecting coronary endothelial dysfunction in patients without CAD (one study), for detecting myocardial ischemia in a RH-PAT exercise test (one study), and for detecting or characterizing CAD (four studies). Four studies investigated RH-PAT for predicting cardiovascular adverse events following a surgical procedure. The results varied across studies and applications due to heterogeneity in patient selection criteria, applications, reference standards, and cut-off values. There were no studies evaluating the impact of the use of RH-PAT on health outcomes. The report concluded that evidence evaluating the clinical validity of reactive hyperemia peripheral arterial tonometry is insufficient to determine its value in the evaluation of coronary artery disease or to predict cardiovascular adverse events.

van den Heuvel et al. (2017) reported on a study of 93 patients to examine the applicability of PAT to detect a low risk of coronary artery disease (CAD) in a chest pain clinic. PAT was performed resulting in reactive hyperaemia (RHI) and augmentation (Alx) indices. Patients were risk classified according to HeartScore, Diamond and Forrester pretest probability (DF), exercise testing (X-ECG), and computed tomography calcium scoring (CCS) and angiography (CTA). Correlations, risk group differences and prediction of revascularisation within 1 year were calculated. The results indicated that PAT cannot detect a low risk of CAD, possibly because RHI and Alx versus X-ECG, CCS and CTA represent independent processes.



To assess whether endothelial dysfunction, as detected by peripheral artery tonometry, can predict late cardiovascular events, Rubinshtein et al. (2010) induced reactive hyperaemia (RH) following upper arm occlusion of systolic blood pressure in 270 outpatients. The natural logarithmic scaled RH index (L\_RHI) was calculated from the ratio between the digital pulse volume during RH and at baseline. Follow-up was seven years. Seven-year adverse event rate was 48% in patients with L\_RHI < 0.4 vs. 28% in those with L\_RHI ≥ 0.4 (p=0.03). Univariate predictors of adverse events were LRHI, advancing age, and prior coronary bypass surgery. Multivariate analysis identified L\_RHI < 0.4 as an independent predictor of AE (p=0.03). Study limitations include an uncontrolled study design, and dropout rate of 17%.

Hamburg et al. (2008) reported results of a correlational cohort study of Framingham Third generation Cohort participants (n=1957). A fingertip peripheral arterial tonometry (PAT) device was used to measure digital pulse amplitude. Measurements were taken at baseline and in 30 second intervals for four minutes during reactive hyperemia induced by five minute forearm cuff occlusion. The relation of PAT ratio to cardiovascular risk factors was strongest in the 90-120 second postdeflation interval (overall model R<sup>2</sup>=0.159). To determine the relation between the hyperemic response over time following cuff deflation and clinical cardiovascular risk factors, stepwise regression models were performed for the PAT ratio for each 30 second interval with age and sex forced in, selecting from systolic blood pressure, diastolic blood pressure, heart rate, body mass index, total/HDL cholesterol, triglycerides, glucose, diabetes, current smoking, hormone replacement therapy, hypertension treatment, lipid-lowering treatment, and prevalent cardiovascular disease. The relation of PAT ratio to cardiovascular risk factors was strongest in the 90-120 second postdeflation interval (overall model R<sup>2</sup>=0.159). The authors note study findings support further investigations to define clinical utility and predictive value of digital pulse amplitude. The study was limited by uncontrolled design.

#### **Professional Societies/Organizations**

**American College of Cardiology Foundation/American Heart Association (ACCF/AHA):** These organizations published the 2010 Guideline for the Assessment of Cardiovascular Risk in Asymptomatic Adults. The guideline notes that it is unclear whether these measures of peripheral endothelial health provide incremental predictive information when controlling for traditional risk factors. The guideline further notes that due to the limited data available, the writing committee concluded that it was premature to recommend serial FMD measurements to monitor treatment effects. In addition, due to the technical challenges of standardizing measurement of FMD and the relatively modest evidence of incremental change in risk assessment, measurement for risk assessment was not regarded as appropriate for risk assessment in the asymptomatic adult.

**American Society of Echocardiography/Society for Vascular Medicine:** These societies (Roman, et al., 2006) published a report regarding the clinical application of noninvasive vascular ultrasound in cardiovascular risk stratification. The report notes that the ability of flow-mediated endothelium-dependent brachial artery dilation to provide prognostic information in individuals at intermediate- or low-risk, independent of more standard risk-profiling approaches, remains to be identified.

#### **Use Outside of the US**

No relevant information.

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### **Coding/Billing Information Cardiovascular**

**Note:** 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

### **Cardiovascular Services Considered Experimental/Investigational/Unproven:**

<b>CPT®*</b> <b>Codes</b>	<b>Description</b>	<b>Comment</b>
<a href="#">33340</a>	Percutaneous transcatheter closure of the left atrial appendage with endocardial implant, including fluoroscopy, transseptal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, when performed, and radiological supervision and interpretation	
<a href="#">34806</a>	Transcatheter placement of wireless physiologic sensor in aneurysmal sac during endovascular repair, including radiological supervision and interpretation, instrument calibration, and collection of pressure data (List separately in addition to code for primary procedure) (Code deleted 12/31/2017)	
<a href="#">34839</a>	Physician planning of a patient-specific fenestrated visceral aortic endograft requiring a minimum of 90 minutes of physician time	
<a href="#">34841</a>	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including one visceral artery endoprosthesis (superior mesenteric, celiac or renal artery)	
<a href="#">34842</a>	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including two visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
<a href="#">34843</a>	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including three visceral artery	



	endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
<a href="#">34844</a>	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including four or more visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
<a href="#">34845</a>	Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including one visceral artery endoprosthesis (superior mesenteric, celiac or renal artery)	
<a href="#">34846</a>	Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including two visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
<a href="#">34847</a>	Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including three visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
<a href="#">34848</a>	Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including four or more visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
<a href="#">92978</a>	Endoluminal imaging of coronary vessel or graft using intravascular (IVUS) or optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; initial vessel (List separately in addition to code for primary procedure)	Considered Experimental/Investigational/Unproven when used to report CPT code 92978 using endoluminal imaging of coronary vessel or graft using optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; initial vessel



<a href="#">92979</a>	Endoluminal imaging of coronary vessel or graft using intravascular (IVUS) or optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; each additional vessel (List separately in addition to code for primary procedure)	Considered Experimental/Investigational/Unproven when used to report CPT code 92979 using endoluminal imaging of coronary vessel or graft using optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; each additional vessel
<a href="#">93799</a>	Unlisted cardiovascular service or procedure	Considered Experimental/Investigational/Unproven when used to report acoustic cardiography
<a href="#">93982</a>	Noninvasive physiologic study of implanted wireless pressure sensor in aneurysmal sac following endovascular repair, complete study including recording, analysis of pressure and waveform tracings, interpretation and report (Code deleted 12/31/2017)	
<a href="#">99199</a>	Unlisted special service, procedure or report	Considered Experimental/Investigational/Unproven when used to report near-infrared guidance for vascular access requiring real-time digital visualization of subcutaneous vasculature for evaluation of potential access sites and vessel patency
<a href="#">0205T</a>	Intravascular catheter-based coronary vessel or graft spectroscopy (eg, infrared) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation, and report, each vessel (List separately in addition to primary procedure)	
<a href="#">0234T</a>	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; renal artery	
<a href="#">0235T</a>	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; visceral artery (except renal), each vessel	
<a href="#">0236T</a>	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; abdominal aorta	
<a href="#">0237T</a>	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; brachiocephalic trunk and branches, each vessel	
<a href="#">0238T</a>	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; iliac artery, each vessel	
<a href="#">0254T</a>	Endovascular repair of iliac artery bifurcation (eg, aneurysm, pseudoaneurysm, arteriovenous malformation, trauma, dissection)	



	using bifurcated endograft from the common iliac artery into both the external and internal iliac artery, including all selective and/or nonselective catheterization(s) required for device placement and all associated radiological supervision and interpretation, unilateral	
<a href="#">0255T</a>	Endovascular repair of iliac artery bifurcation (eg, aneurysm, pseudoaneurysm, arteriovenous malformation, trauma) using bifurcated endoprosthesis from the common iliac artery into both the external and internal iliac artery, unilateral; radiological supervision and interpretation (Code deleted 12/31/2017)	
<a href="#">0266T</a>	Implantation or replacement of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intraoperative interrogation, programming, and repositioning, when performed)	
<a href="#">0267T</a>	Implantation or replacement of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming and repositioning, when performed)	
<a href="#">0268T</a>	Implantation or replacement of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)	
<a href="#">0269T</a>	Revision or removal of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)	
<a href="#">0270T</a>	Revision or removal of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)	
<a href="#">0271T</a>	Revision or removal of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)	
<a href="#">0272T</a>	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (eg, battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day);	
<a href="#">0273T</a>	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (eg, battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day); with programming	
<a href="#">0337T</a>	Endothelial function assessment, using peripheral vascular response to reactive hyperemia, non-invasive (eg, brachial artery ultrasound, peripheral artery tonometry), unilateral or bilateral	

<b>HCPCS Codes</b>	<b>Description</b>
<a href="#">C2624</a>	Implantable wireless pulmonary artery pressure sensor with delivery catheter, including all system components
<a href="#">C9741</a>	Right heart catheterization with implantation of wireless pressure sensor in the pulmonary artery, including any type of measurement, angiography, imaging supervision, interpretation, and report

\*Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.



## **Pulmonary**

### **Computer-Aided Detection of Chest Radiographs (CPT Codes 0174T, 0175T)**

Computer-aided detection (CAD) systems for computed tomography or digital chest x-rays are software programs that subtract one lung from another to reveal subtle asymmetric opacities, and perform temporal subtraction of prior imaging from the current exam. The basic concept of computer-aided detection (CAD) is to provide computerized image recognition to assist and improve radiologist's interpretation. Through algorithms, CAD technology provides radiologists with regions of interest (ROI) for their interpretation. Although CAD is used most often in mammography, many different types of CAD technologies and/or devices are being developed for detection of various lesions in medical imaging, including conventional x-ray, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound.

Proponents of computer-aided detection with chest x-ray state that diagnostic accuracy is improved with the use of a CAD program and that CAD can expedite screening of at-risk individuals at an earlier and more curable stage of lung cancer. Potential risks of using CAD with chest x-rays may include the generation of false-positive and false-negative results leading to over- and under-diagnosis. Abnormalities (e.g., scars from smoking, areas of inflammation, or other noncancerous conditions) can mimic lung cancer on x-ray. Subsequent additional testing may cause anxiety for the patient or may lead to unnecessary biopsy or surgery and increase medical costs. Also, the use of CAD programs in screening for lung cancer may detect small tumors that would never become life-threatening, putting a patient at risk for unnecessary treatments for cancer, such as chemotherapy or radiation.

### **U.S. Food and Drug Administration (FDA)**

Deus Technologies received FDA premarket approval for its RapidScreen™ CAD system in July 2001. Its intended use is "to identify and mark regions of interest on digital or digitized frontal chest radiographs. It identifies features associated with solitary pulmonary nodules from 9–30 millimeters (mm) in size, which could represent early-stage lung cancer. The device is intended for use as an aid only after the physician has performed an initial interpretation of the radiograph. The device is of little value when used for patients who are not at high risk for lung cancer."

In 2007, Deus Technologies manufacturer Riverain Medical Group (Miamisburg, OH) received approval for a new trade name. The device, as modified, will be marketed under the trade name OnGuard™ and is indicated "to identify and mark ROIs on frontal chest radiographic films from adult males with an increased risk for lung cancer to bring ROI to the attention of the radiologist after the initial reading has been completed. Thus the system assists the radiologist in minimizing observational oversights by identifying areas on the original chest films that may warrant a second review." In March of 2012, Riverain's OnGuard software was renamed ClearRead Detect™. Currently, Riverain Medical's ClearRead Detect™ CAD System is the only FDA-approved CAD systems with a Product Device Description of "Analyzer, Medical Image" for chest x-rays (Product Code MYN). Other CAD systems (for example, mammography or lung computed tomography) are listed under this same device description.

The FDA approved EDDA Technology's (Princeton Junction, NJ) "IQQA® Chest Software Package" in October 2004 under the Product Device Description of Picture Archiving and Communications System (PACS). It uses a real-time interactive pulmonary nodule analysis system for chest digital radiographic image softcopy reading. Intended use states it is "used during the review of digital chest radiographic images. Combining image viewing, evaluation and reporting tools, the software is designed to support the physician in the identification of lung lesions (e.g. nodules), as well as the confirmation, evaluation and documentation of such physician-identified lesions. The IQQA-Chest software package supports a workflow based on automated segmentation for the visual identification of possible lesions. The tools also allow for regional analysis of possible lesions in terms of size, shape and position, thus aiding the physician in the characterization of physician-identified suspicious lesions." Philips Medical Systems (Hamburg, Germany) has licensed EDDA Technology's IQQA® Chest software and markets it under the name xLNA (x-ray lung node assessment) Enterprise.

### **Literature Review**



There is insufficient evidence in the published, peer-reviewed scientific literature addressing the accuracy and clinical utility of CAD of chest x-rays. Well-designed clinical trials are lacking. Studies are primarily retrospective analyses of registry data and there is concern regarding unacceptable false-positive rates. Retrospective registry studies address multiple variables that may impact accuracy such as the experience and training of radiologist using the CAD program, type of chest x-ray utilized (e.g., temporal subtraction, dual energy subtraction) and region of interest identification parameters in the algorithms themselves (e.g., nodules size, bone suppression, and nodule-in-center or nodule-in-circle criterion). Additionally, screening populations and timing for the use of CAD in the diagnostic work-up vary in studies. The clinical utility of CAD of chest x-rays for lung cancer screening is not established. The FDA wording regarding RapidScreen™ CAD systems notes that the device is of little value when used for patients who are not at high risk for lung cancer (Dellios, et al., (2017); Kligerman, et al., 2013; De Boo, et al., 2011; Meziame, et al., 2012; Szucs-Farkas, et al., 2010; Balkman, et al., 2010; Moore, et al., 2010; White, et al., 2009; Li, et al., 2008; Van Beek, et al., 2008; Bley, et al., 2008; Kakeda, et al., 2004).

### **Professional Societies/Organizations**

**American College of Radiology (ACR):** ACR (Mohammed, et al., 2013) published appropriateness criteria for the screening of pulmonary metastases. According to the ACR, computer-aided detection (CAD) for pulmonary metastatic disease has been adapted to chest CT. Although these programs are in their developmental phases, the ACR notes it has been suggested that CAD can be used as a second look after the radiologist has completed reviewing the study. However, the ACR notes these applications require more development and can only be used when there is limited breathing artifact and stable lung expansion. CAD is still in the investigative phase and has limited use in evaluating patients with pulmonary metastatic disease.

### **Use Outside of the US**

No relevant information.

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### **Intermittant and Continuous Measurement of Wheeze Rate for Bronchodilator or Bronchial Challenge (CPT code 94799)**

The American Thoracic Society Committee on Pulmonary Nomenclature defines wheezing as high-pitched (dominant frequency of  $\geq 400$  Hz) continuous adventitial lung sounds (i.e.,  $>250$ msec) (Schraufnagel and Murray, 2010). The sound is generated by turbulence in larger airways that collapse with forced expiration (Boat and Green, 2011). Repeated examination may be required to verify a history of wheezing and should be directed toward assessing air movement, ventilatory adequacy, and evidence of chronic lung disease (Boat and Green, 2011). Computerized lung sound analysis involves recording the patient's lung sounds via an electronic device, followed by computer analysis and classification of lung sounds based on specific signal characteristics. Intermittant measurement of wheeze rate by pulmonary sound analysis has been proposed for use in bronchodilator or bronchial challenge diagnostic evaluation. Continuous measurement of wheeze rate by sound analysis has been proposed during treatment assessment such as bronchodilator or bronchial challenge evaluations, and during sleep for documentation of nocturnal wheeze and cough.

### **U.S. Food and Drug Administration (FDA)**

Several devices have received FDA approval for the measurement of wheeze rate. The PulmoTrack™ 2020 System (iSonea, formerly KarmelSoniz, Binyamina, IS, US office: Alta Loma, CA) received 510(k) approval in March 2011. The approval summary notes "The PulmoTrack™ 2020 is intended for the analysis, interpretation and documentation of lung sounds. The PulmoTrack™ 2020 is indicated for use by or under the supervision of a physician while carrying out a provocation test, administering a bronchodilator or performing a physical examination in pulmonary function testing environment when there is a need for performing an acoustic pulmonary function measurement that quantifies the presence of wheezing. It is also indicated when there is a need to listen to amplified and filtered breath sounds. The PulmoTrack™ 2020 is indicated for patient population above two years old." The WIM-PC received 510(k) approval in November 2007. The FDA summary notes "The WIM-PC is intended for the analysis, interpretation and documentation of lung sounds."

### **Literature Review**

Randomized controlled clinical trial data in the published peer-reviewed scientific literature are scarce to inform the effectiveness and clinical utility of wheeze rate measurement. Gurung et al. (2011) performed a systematic review and meta-analysis to estimate the sensitivity and specificity of computerized lung sound analysis for the detection of lung sounds. Eight studies were selected for review. Overall sensitivity for the detection of wheezes or crackles was 88%, and specificity was 85%. The authors noted there is a lack of standardization across studies in the methods used for lung sound recording, computer algorithms for signal analysis and statistical methods for outcome analysis. Further research is needed to address the effectiveness of specific combinations of electronic devices and computing algorithms in clinical and community settings.

Beck et al. (2007) evaluated the use of computerized quantification of wheezing and crackles compared to a clinical score in assessing the effect of inhaled albuterol or inhaled epinephrine in infants with RSV bronchiolitis



during a double blind, randomized, controlled nebulized treatment pilot study. Computerized quantification of wheezing and crackles (PulmoTrack) and a clinical score were performed prior to, 10 minutes post and 30 minutes post treatment. Breath segments containing at least five consecutive interference-free breaths were analyzed for a total of 20 breaths. Wheeze Rate (percent of time wheezing of total breath time) and crackle count (number of crackles per breath) were determined by the PulmoTrack® for each breath cycle, and averaged over the 20 breaths. Satisfactory lung sounds recording and analysis was achieved in all subjects. There was no significant change in objective quantification of wheezes and crackles or in the total clinical scores either within the groups or between the groups. Although data suggest that automated wheeze rate measurement is feasible, the authors note that a larger study is necessary to assess the correlation between the computerized crackle and wheeze counts and the Clinical Score in response to treatment in RSV bronchiolitis.

#### **Use Outside of the US**

No relevant information.

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#### **Cryoablation of Lung Tumors (CPT Code 0340T, 32994) (Code 0340T deleted 12/31/2017; use 32994 to report)**

Pulmonary tumor cryoablation involves the destruction of tumor tissue using extreme cold. This is also known as cryoablation, cryosurgery, or cryotherapy. In this procedure a small thin wand-like needle, known as a cryoprobe, is inserted through the skin of the chest and between the ribs. Under computerized tomography (CT) guidance, the probe is advanced into the lesion of the lung and any tumor extensions to the pleura and/or chest wall. Compressed argon gas is passed through the probe and into the tumor, which freezes it and destroys the tissue. Treatment with the probe usually takes several minutes and may include repositioning the probe within the lesion so that overlapping ablations treat the entire tumor.

#### **Literature Review**

Randomized controlled clinical trial data are lacking in the published peer-reviewed scientific literature to demonstrate the safety and effectiveness of pulmonary tumor ablation by cryoablation. Studies are limited by uncontrolled design and small patient populations. Additional well-designed high quality studies are necessary to inform on health outcomes. Further, published professional consensus is necessary before this treatment can be translated into routine clinical practice.

Moore et al. (2015) reported on a retrospective study that evaluated long-term survival in 45 patients with early stage non-small cell lung cancer (NSCLC) treated with cryoablation treatment. The study findings included five year survival rate 67.8% ± 15.3; the cancer-specific survival rate was 56.6% ± 16.5; and the 5-year progression-free survival rate was 87.9% ± 9. The combined local and regional recurrence rate was 36.2%. Major



complications occurred 6.4% of patients that included two cases of hemoptysis and a prolonged placement of a chest tube requiring mechanical sclerosis in one patient. There were no deaths in the first 30 days after treatment.

Hayes published a technology directory report regarding cryoablation for treatment of non-small cell lung cancer (NSCLC) (Hayes, 2015; 2017). The review included one randomized controlled trial (RCT), six nonrandomized comparative studies, and one uncontrolled study, with sample size of 36 to 346 patients. The body of evidence concerning cryoablation for NSCLC is moderate in size and low in overall quality. Results of the available studies provide preliminary evidence that cryoablation is a reasonably safe and effective treatment for NSCLC. While the results of some of the studies were somewhat conflicting or inconclusive, there is some evidence of improved survival when cryoablation is used alone or with other therapies. Additional well-designed studies with long-term follow-up are needed to define the clinical role of cryoablation relative to other common therapies for NSCLC such as surgery, RFA, chemotherapy, radiation therapy, and immunotherapy.

Yashiro et al. (2013) reported results of a prospective study of 71 consecutive patients with 210 pulmonary tumors treated with 102 sessions of percutaneous cryoablation of lung tumors. A mean of 1.4 sessions was performed per case. A maximum of four cryoprobes was used on one lesion; the number and diameter of the probes were based on estimated tumor size. Every procedure was performed using a triple freeze/thaw protocol. High-pressure argon gas was used for freezing. There was no procedural mortality. Of 210 tumors, technical success was achieved for 167 (79.5%). At a median follow-up of 454 days, local progression occurred in 50 tumors (23.8%). One-, 2-, and 3-year local progression-free rates were 80.4%, 69.0%, and 67.7%, respectively, and technique effectiveness rates were 91.4%, 83.0%, and 83.0%, respectively. Existence of a thick vessel (diameter  $\geq 3$  mm) no more than 3 mm from the edge of the tumor was assessed as an independent factor (HR, 3.84; 95% CI, 1.59–9.30;  $P = .003$ ) associated with local progression by multivariate analysis. Although results are promising, study limitations include uncontrolled design, and small patient numbers.

Kawamura et al. (2006) conducted a nonrandomized uncontrolled study to evaluate cryoablation of 35 pulmonary metastatic tumors in 20 patients who were not surgical candidates. In all cases cryoablation was performed percutaneously under CT guidance with local anesthesia. A total of 22 sessions of cryoablation were performed. Pneumothorax occurred in 11 of the 22 sessions, primarily after the completion of the ablation procedure. A chest tube was inserted in one case, transient needle aspiration was performed in three cases, and in seven cases no additional treatment was given. Phrenic nerve palsy occurred during one session. Mean hospital stay after treatment was 2.6 days, although for the initial five sessions, it was 5.4 days. There were no treatment-related deaths or conversion to surgical intervention. The follow-up period was 9 to 28 months. Local recurrence occurred in 7 (20%) of tumors. Five patients underwent repeat cryoablation without complications. Study limitations which preclude the ability to apply results to other populations include uncontrolled randomized design and small study populations.

### Professional Societies/Organizations

**National Comprehensive Cancer Network™ (NCCN™):** The NCCN (2017) guidelines do not contain detailed information on cryoablation for NSCLC. Cryotherapy is briefly mentioned as follows (NCCN, 2017):

- Resection is the preferred local treatment modality (other modalities include radiotherapy ablation, cryotherapy, and stereotactic ablative radiotherapy).

### Use Outside of the US

**European Society for Medical Oncology (ESMO):** ESMO published clinical practice guidelines for metastatic non-small cell lung cancer (Novello, et al., 2016). The guidelines note that in case of symptomatic major airways obstruction or postobstructive infection, endoscopy debulking by laser, cryotherapy or stent placement may be helpful (III, C).

Levels of evidence and grades of recommendation

III Prospective cohort studies

C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs), optional

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### **Coding/Billing Information Pulmonary**

**Note:** 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

### **Pulmonary Services Considered Experimental/Investigational/Unproven:**

<b>CPT® Codes</b>	<b>Description</b>	<b>Comment</b>
<a href="#">32994</a>	Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging guidance when performed, unilateral; cryoablation	
<a href="#">94799</a>	Unlisted pulmonary service or procedure	Considered Experimental/Investigational/Unproven when used to report intermittent measurement of wheeze rate for bronchodilator or bronchial challenge diagnostic evaluation
<a href="#">0174T</a>	Computer aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed concurrent with primary interpretation (List separately in addition to code for primary procedure)	
<a href="#">0175T</a>	Computer aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed remote from primary interpretation	
<a href="#">0340T</a>	Ablation, pulmonary tumor(s), including pleura or chest wall when involved by tumor extension, percutaneous, cryoablation, unilateral, includes imaging guidance (Code deleted 12/31/2017)	

**\*Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.**



## **Gastroenterology**

### **Fecal Calprotectin Testing (FC) (CPT Code 83993)**

This laboratory test measures the level of calprotectin in stool. Calprotectin is a calcium and zinc binding protein that is found predominantly in neutrophils. The concentration of calprotectin is higher in feces compared to plasma and can be measured by enzyme-linked immunosorbent assay (ELISA) using less than five grams of stool. Although the normal range has been defined for FC, an optimal cutoff point for distinguishing inflammatory bowel disease (IBD) from other diagnoses has not been defined (von Roon et al. 2007). It has been studied as a surrogate marker of intestinal inflammation in inflammatory bowel diseases (e.g., Crohn's disease, ulcerative colitis), colorectal cancer, diverticular disease, and polyposis of the colon. It has also been studied as a marker to predict response to treatment and relapse of disease.

### **U.S. Food and Drug Administration (FDA)**

PhiCal™ Fecal Calprotectin Immunoassay (Genova Diagnostics, Inc., Ashville, NC) received Class II device approval in 2006. The immunoassay is a lab test that measures the amount of fecal calprotectin in a patient's stool sample. The PhiCal test is indicated for use as an in vitro diagnostic to aid in the diagnosis of inflammatory bowel diseases (IBD) (Crohn's disease and ulcerative colitis), and to differentiate IBD from irritable bowel syndrome (IBS) when used in conjunction with other diagnostic testing and the total clinical picture.

### **Literature Review**

Randomized controlled clinical trial data are lacking regarding the clinical utility of fecal calprotectin testing to inform diagnosis, or predict relapse or response to treatment for IBD or any indication. Although patient numbers included in published studies are large, a number of study limitations have been identified by authors including uncontrolled and heterogeneous study design, and heterogeneous patient populations. Further, in some studies it is unknown whether FC samples were obtained before commencing treatment, which may be a major confounder in reports of diagnostic accuracy (Henderson, et al., 2013). In the study by Henderson (2013) the authors note "The assessment of methodological quality determined that there were deficiencies in all the studies evaluated, but especially with regard to important aspects, such as the use of a representative spectrum of patients, an acceptable reference standard (upper and lower endoscopy), and the poor reporting of current treatment modalities in use during FC sampling."

**Inflammatory Bowel Disease (IBD):** El-Matary et al. (2017) reported on a retrospective cohort study that examined the impact of fecal calprotectin (FCal) measurements on decision-making and clinical care of children with IBD. FCal, clinical activity indices, and blood markers were measured in 77 (115 fecal samples) children with diagnoses of IBD. Pearson correlation coefficient analysis was performed to examine association between FCal and other markers. Then decisions based on FCal measurements were prospectively documented and participants were evaluated three to six months later. FCal positively correlated with clinical activity indices ( $r = 0.481$ ,  $P < 0.05$ ) and erythrocyte sedimentation rate ( $r = 0.40$ ,  $P < 0.05$ ) and negatively correlated with hemoglobin ( $r = -0.40$ ,  $P < 0.05$ ). Sixty-four out of 74 (86%) positive FCal measurements ( $\geq 250$   $\mu\text{g/g}$  of stools) resulted in treatment escalation with subsequent significant clinical improvement while in the FCal negative group, 34 out of 41 (83%) measurements resulted in no change in treatment and were associated with remission on follow-up. The study was limited by lack of randomization, retrospective design, and small sample size in particular for those for those who had colonoscopy.

Abej et al. (2016) reported on a prospective cohort study performed to determine the relationship between fecal calprotectin (FCAL) and imaging studies and other biochemical inflammatory markers and the impact of FCAL measurements on decision-making in IBD patient management in usual clinical practice. The study included 240 persons with IBD. The correlation between FCAL values and other markers for disease activity such as serum albumin (alb), hemoglobin (Hg), and C-reactive protein (CRP) and diagnostic imaging or colonoscopy were examined. FCAL  $\geq 250$  mcg/g of stool was considered a positive result indicating active IBD. The results of 183 stool samples (76.3%) were returned. The return rate in the pediatric and adult cohorts was 91% ( $n = 82$ ) and 67.3% ( $n = 101$ ), respectively ( $P < 0.0001$ ). Positive FCAL was associated with colonoscopy findings of active IBD ( $P < 0.05$ ), low albumin ( $P < 0.05$ ), anemia ( $P < 0.01$ ), and elevated CRP ( $P < 0.01$ ). There was no significant difference for FCAL results by outcomes on small bowel evaluation among the 21 persons with small bowel CD.



Most persons (87.5%) with normal FCAL and no change in therapy remained in remission during subsequent 3 months. Of 11 subjects with a positive FCAL who underwent imaging, only 6 had active disease on imaging; a positive FCAL was not significantly associated with radiologic evidence of active disease ( $P = 0.31$ ). This study was limited by lack of controls, and the small number who underwent imaging and endoscopy.

Bar-Gil Shitrit et al. (2016) reported on a study that prospectively assessed the value of fecal calprotectin and lactoferrin in 68 patients with Crohn's disease (CD) to predict capsule endoscopy (CE) findings. Stool samples for calprotectin and lactoferrin and blood samples were collected for relevant parameters. Correlation between fecal markers and CE findings was assessed and receiver operating characteristic (ROC) curves were built to determine the predictive values of fecal markers for the diagnosis of CD. Fecal calprotectin data was available for all the patients and lactoferrin data for 38. CE findings compatible with CD were found in 23 (33%) patients and 45 (67%) were negative for CD. The average age of the CD group was 34 compared to 46 in the non-CD group ( $p = .048$ ). Median calprotectin and lactoferrin in the CD group and in the control group were 169 mg/kg vs. 40 ( $p = .004$ ) and 6.6 mg/kg versus 1 ( $p = .051$ ), respectively. The area under the ROC curve was 0.767 for calprotectin and 0.70 for lactoferrin. A fecal calprotectin concentration of 95 mg/kg and fecal lactoferrin of 1.05 mg/kg had a sensitivity, specificity, positive predictive value and negative predictive value of 77 and 73%, 60 and 65%, 50 and 50%, and 84 and 84% in predicting CE findings compatible with CD. The study is limited by small number of participants and lack of controls.

Several meta-analyses of prospective and registry data have been performed to examine the predictive capacity of fecal calprotectin in individuals with IBD (e.g., Crohn's disease, ulcerative colitis). Reported results have been inconsistent with a wide variation in sensitivity and specificity of FC for included studies, ranging from 61-100% and 71-100%, respectively for diagnosis of IBD and other intestinal disorders. Sensitivity and specificity to predict relapse are 43-80% and 48-73%, respectively (Heida, et al., 2017; Henderson, et al., 2013; Kostakis, et al., 2012; Mao, et al., 2012; Jellema, et al., 2011; Laharie, et al., 2011; van Rheenen, et al., 2010; von Roon, et al., 2007).

In several studies (Hukkinen, et al., 2016; Henderson, et al., 2013; van Rheenen, et al., 2010), results regarding specificity of FC testing in children were significantly different compared with those for adults (96% and 68-97%, respectively). In addition, recent studies and meta-analysis have been published regarding the use of fecal calprotectin in management of IBD (Bressler, et al., 2015; Wright, et al., 2015; Kennedy, et al., 2015; Mosli, et al., 2015; Menees et al., 2015; Lin, et al., 2014; Sandborn, et al., 2016; Chey, et al., 2015). These studies examine the accuracy of the test, but do not indicate the clinical utility of fecal calprotectin in the management of IBD. The tests did not substantiate the use of this test in altering the management of the condition, or reducing or eliminating other testing for the condition.

Hayes published a directory report for fecal calprotectin (FC) assay for monitoring postoperative recurrence (PER) of Crohn Disease (CD) (2013, 2017). It was found that overall quality of the body of evidence pertaining to the use of FC testing systems for the evaluation of postoperative endoscopic recurrence (PER) in patients with CD was considered to be low with one study rated as good quality; five as fair quality; and, five as poor quality. The major individual study limitations included small sample sizes; study design; lack of blinding; no follow-up; unclear, extended, or varying lengths time between FC stool sample collection and colonoscopy; lack of correction for multiplicity in analysis; multiple endoscopic procedures per patient unaccounted for in the analysis; and nonuniform postoperative treatment. The study concluded that the available evidence indicates that FC testing generally has high negative predictive value (NPVs) and moderate sensitivity but low-to-moderate specificity and positive predictive value (PPVs) for the prediction of PER in patients with CD. With a high NPV, patients and clinicians can have a high assurance that a negative result on an FC test suggests that PER will not occur, thus potentially avoiding or delaying invasive endoscopic procedures. The study noted that however, NPVs and sensitivity values varied across some studies; thus, additional research is needed to define uniform and optimal cutoffs for FC testing to predict and monitor PER of CD. In addition, no direct evidence was available regarding the clinical utility of FC testing to change management or improve outcomes in patients with CD following ileocolic resection. Additional good-quality, blinded studies of sufficient size, design, and duration are required to evaluate the clinical utility of FC testing for monitoring PER of CD.

Hayes published a directory report for the use of fecal calprotectin (FC) assay for monitoring disease activity in Crohn disease (CD) (Hayes, 2013; 2017). The review found that in general, FC testing provides moderate-to-



high sensitivity, specificity, PPV, NPV, and diagnostic accuracy for the prediction of disease activity using endoscopic or clinical indices in patients with CD and that no studies directly addressed measures of clinical utility. The conclusions of the report included that:

- The available evidence suggests that FC testing is safe and may have promise for monitoring disease activity due to the moderate-to-high diagnostic sensitivity and accuracy of this test to predict disease activity in patients with CD. However, no direct evidence was available regarding the clinical utility (i.e., change in patient management or improved clinical outcomes) of FC testing for monitoring disease activity in patients with CD. In addition, the specificity, positive predictive value (PPVs), and negative predictive value (NPVs) varied across studies, and additional studies are required to define uniform cutoffs for FC testing to predict and monitor CD activity.
- Across 12 studies assessing FC testing for the prediction of endoscopic disease activity, sensitivity ranged from 70% to 94.1% and specificity ranged from 40% to 97%. PPV and NPV ranged from 48.5% to 98% and 40% to 96.6%, respectively. Four studies reported diagnostic accuracy, which ranged from 71% to 87%.
- In three studies, FC testing had 50% to 80% sensitivity and 74.4% to 88% specificity for monitoring changes in clinical disease activity. PPV and NPV ranged from 27.6% to 76% and 71% to 96.8%, respectively.
- In one study, FC testing had a moderately high specificity (82%), moderate NPV (75%), and very low sensitivity (37%) for detection of clinical loss of response (LOR) to infliximab in patients undergoing maintenance therapy.
- There do not appear to be any safety concerns with the use of FC testing to predict and monitor CD activity, although the potential risk for false-positive results could result in unnecessary endoscopic procedures.
- Additional good-quality, blinded studies of sufficient size, design, and duration in well characterized patient populations are required to evaluate the clinical utility of FC testing for monitoring disease activity in patients with CD.

Although several clinical trials reflect abnormal or elevated FC levels in individuals with inflammatory bowel disease compared with controls, the clinical utility of fecal calprotectin testing to impact management and improve overall health outcomes has not been demonstrated. Large randomized controlled trials are necessary to establish the role of FC testing when compared to available diagnostic tests.

**Colorectal Cancer:** Similar to IBD, RCT data are lacking in the published, peer-reviewed scientific literature to evaluate the clinical utility of FC testing for screening and diagnosis of colorectal cancer (CRC) in adults and children. Although levels of fecal calprotectin may be elevated in individuals with CRC compared with healthy control subjects, several meta-analyses of prospective and retrospective studies reflect inconsistent sensitivity and specificity with values of 36-75% and 64-84% respectively (von Roon, et al., 2007; Shitrit, et al., 2007). The role of FC testing as a means to diagnose CRC has not been established.

**Other Intestinal Conditions:** FC testing has also been proposed for other conditions such as irritable bowel syndrome, colonic polyposis, diverticular disease, and diarrhea (Tursi, et al., 2014; Licata, et al., 2012; Pezzilli, et al., 2008; Parsons, et al., 2014). Randomized controlled trial data are lacking in the published peer-reviewed scientific literature demonstrating the ability to impact care management or improve patient health outcomes with FC testing. Further, there is a lack of published literature reflecting that this is considered a standard of care option for these indications. At this time there is insufficient evidence to determine the role and clinical utility of such testing.

### Professional Societies

**American College of Gastroenterology (ACG):** ACG published updated guidelines for management of Crohn's Disease in adults (Lichtenstein, et al., 2018). The guidelines include the following recommendation:

- Diagnosis: Fecal calprotectin is a helpful test that should be considered to help differentiate the presence of IBD from irritable bowel syndrome (IBS) (strong recommendation, moderate level of evidence).
- In patients who have symptoms of active Crohn's disease, stool testing should be performed to include fecal pathogens, *Clostridium difficile* testing, and may include studies that identify gut inflammation such



as a fecal calprotectin and may include studies that identify gut inflammation such as a fecal calprotectin.(summary statement , no level of evidence)

- Fecal calprotectin and fecal lactoferrin measurements may have an adjunctive role in monitoring disease activity. .(summary statement , no level of evidence)

Level of evidence:

Moderate: (further research would be likely to have an impact on the confidence in the estimate of effect)

Recommendation grading:

Strength of a recommendation graded as “strong” when the desirable effects of an intervention clearly outweigh the undesirable effects.

Summary statements are descriptive and do not have associated evidence-based ratings.

**American Gastroenterological Association (AGA):** the AGA published a clinical care pathway for Crohn’s disease. In the section for assessing inflammatory status, fecal calprotectin is listed along with other lab testing that includes CBC, CRP, CMP, and ESR. There is no evidence level included in the clinical care pathway.

#### Use Outside of the US

**European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN)/North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN):** In joint recommendations From these organizations fecal calprotectin (FC) and fecal leukocytes (FL) are described as markers of bowel inflammation that have been shown to correlate with clinical measures of disease activity in patients who have Crohn’s disease. They note that they may help clinicians ascertain the nature and severity of disease, in particular if prior measurements are available for comparison. Although FC and FL have also been shown to have potential to predict relapse, there is insufficient evidence to recommend routine use of these markers for surveillance of Crohn’s disease (Rufo et al., 2012).

**National Institute for Health and Care Excellence (NICE):** NICE published guidance for fecal calprotectin diagnostic tests for inflammatory diseases of the bowel (2013; 2017). Recommendations include:

- Fecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) in adults with recent onset lower gastrointestinal symptoms for whom specialist assessment is being considered, if:
  - Cancer is not suspected, having considered the risk factors (for example, age) described in the NICE guideline on suspected cancer
  - Appropriate quality assurance processes and locally agreed care pathways are in place for the testing.
- Fecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of IBD or non-IBD (including IBS) in children with suspected IBD who have been referred for specialist assessment, if:
  - Appropriate quality assurance processes and locally agreed care pathways are in place for the testing.

**World Gastroenterology Organisation (2015):** The global guideline for irritable bowel syndrome (IBS), lists fecal inflammation marker (e.g., calprotectin) in the IBS Level I diagnostic cascade.

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**Transanal Radiofrequency Therapy for Fecal Incontinence (e.g., SECCA Procedure) (CPT Code 46999)**



Fecal incontinence is the inability to control the passage of gas, liquid and/or solid feces due to the loss of the coordinated function of the muscles and/or nerves of the rectum, anal canal, and pelvic floor. Treatment of minor incontinence (i.e., incontinence to flatus and occasional seepage of liquid stool) may be controlled by changes in diet and dietary habits, medication (e.g., bulking agents, antidiarrheal drugs), and bowel training (e.g., Kegel exercises, biofeedback). In the case of major incontinence (i.e., frequent loss of solid waste material) or incontinence unresponsive to conservative measures, surgical intervention may be indicated. In the event of an isolated sphincter defect, the standard surgical treatment is sphincteroplasty. Other surgical procedures include repair of rectocele or rectal prolapse and, in severe cases, fecal diversion (i.e., colostomy) (Kim, et al., 2009; Lefebure, et al., 2008; Rao, 2004; Wexner and Sands, 2003; Takahashi, et al., 2002).

Transanal radiofrequency therapy (e.g., Secca® procedure) is a proposed alternative therapy for the treatment of fecal incontinence for patients who have not responded to medical therapy and are not good surgical candidates or have failed surgical intervention. The Secca procedure is noninvasive, typically takes 30–45 minutes, and is performed in an outpatient setting under local anesthesia and sedation. It is also proposed that there are fewer complications following the Secca procedure compared to invasive surgical procedures.

Radiofrequency therapy is based on the theory that “collagen deposition and subsequent scarring may increase one’s ability to recognize and retain stool and permit improved continence” (Parisien and Corman, 2005). An anoscopic device uses four electrodes to deliver controlled radiofrequency energy to the sphincter muscles surrounding the anal canal. The energy creates precise, submucosal burn lesions, triggering collagen contraction. The lesions are subsequently resorbed, remodeling the tissue. The remodeling is proposed to improve barrier function of the anal sphincter (Efron, et al., 2003; Takahashi, et al., 2002).

#### **U.S. Food and Drug Administration (FDA)**

The Secca® System (Curon Medical Inc., Sunnyvale, CA) was approved by the FDA as a 510(k) Class II device for general use for electrosurgical coagulation and “for use specifically in the treatment of fecal incontinence in those patients with incontinence to solid or liquid stool at least once per week and who have failed more conservative treatment” (FDA, 2002).

#### **Literature Review**

The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review for treatments for fecal incontinence (Forte, et al., 2016). The review found only case series studies for SECCA procedure, no randomized controlled trials or observational studies were found. It was found that evidence was insufficient regarding this procedure.

There is insufficient evidence in the published peer-reviewed scientific literature to support the effectiveness of transanal radiofrequency therapy (e.g., Secca procedure) for the treatment of fecal incontinence. Studies are primarily in the form of prospective case series with small patient populations (n=8–50). With the exception of one, five-year study (Takahashi-Monroy, et al., 2008) follow-ups were short-term, ranging from 6–12 months. Various questionnaires (e.g., Fecal Incontinence Severity Index, Fecal Incontinence-related Quality of Life questionnaire, Vaizey scale) were utilized to measure quality of life (e.g., coping, depression, embarrassment) outcomes and results were inconsistent. Typically there were no significant improvements in physical component outcomes, such as anorectal manometry parameters, pudendal nerve motor latency, endoanal ultrasound results, and the thickness of internal anal sphincters. Some studies reported numerous complications while others reported no complications (Ruiz, et al., 2010; Kim, et al., 2009; Lefebure, et al., 2008; Takahashi-Monroy, et al., 2008; Felt-Bersma, et al., 2007; Efron, et al., 2003; Takahashi, et al., 2003). Studies comparing the use of transanal radiofrequency therapy to established medical and surgical treatment options are lacking.

#### **Professional Societies/Organizations**

**American College of Gastroenterology (ACG):** in the ACG clinical guideline for management of benign anorectal disorders (Wald, et al., 2014) for the treatment of fecal incontinence it is noted regarding the Secca procedure, that there is insufficient evidence to recommend radiofrequency ablation treatment to the anal sphincter (SECCA) at this time (no recommendation, insufficient evidence).



**American Society of Colon and Rectal Surgeons:** In their practice parameters for the treatment of fecal incontinence, the American Society of Colon and Rectal Surgeons (Tjandra, et al., 2007) discussed the medical (e.g., fiber intake, antidiarrheal agents, enemas, laxatives, suppositories, anal plug) and surgical (e.g., sphincter repair, injectable therapy, sacral nerve stimulation, dynamic graciloplasty, artificial bowel sphincter, stoma) treatment options for this condition. Based on studies by Takahashi et al. (2003) (n=10) and Efron et al. (2003) (n=50), the ASCRS stated that the Secca procedure may be useful for selected patients with moderate fecal incontinence.

#### **Use Outside of the US**

**National Institute for Health and Care Excellence (NICE):** In an interventional procedure guidance document, NICE (2011) (United Kingdom) stated that endoscopic radiofrequency therapy of the anal sphincter for the treatment of fecal incontinence raised no major safety concerns, but the procedure should only be carried out in units specializing in the assessment and treatment of fecal incontinence. NICE noted that further research is needed to clearly define the appropriate patient group for this procedure. The guidance was based on three case series with small patient populations (n=19–50).

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**Endoscopic retrograde cholangiopancreatography (ERCP), with optical endomicroscopy (CPT code 0397T)**

Optical microscopy, also known as confocal laser endomicroscopy (CLE), is an emerging endoscopic technology that permits high-resolution assessment of gastrointestinal mucosal histology at a cellular and sub-cellular level. CLE and endocytoscopy can be performed with probe-based systems that are passed through the working channel of an endoscope. A confocal miniprobe is a flexible probe-based system (Cellvizio, Mauna Kea Technologies, Paris, France) that is used as an alternative to a confocal laser endomicroscope. In probe-based confocal laser endomicroscopy (pCLE), both the laser scanning unit and light source are outside the body of the patient, which makes the confocal miniprobe a "passive" conduit. The miniprobes are very flexible and can be passed through the working channel of a standard endoscope. The indications for confocal laser endomicroscopy (CLE) are still being defined. In general, the technology is used to target biopsies of abnormal tissue and to avoid taking biopsies of normal tissue. A use of this technology that is being investigated is the differentiation of benign from malignant biliary strictures with probe-based CLE (Meining, [UpToDate], 2017).

**U.S. Food and Drug Administration (FDA)**

In 2012 the Cellvizio® 100 Series System and Cellvizio® System with Confocal Miniprobes received 510(k) premarket approval for the GastroFlex M" series of Confocal Miniprobes" which are intended to allow imaging of the internal microstructure of tissues in the upper gastrointestinal tract including biliary and pancreatic ducts, accessed by an endoscope or endoscopic accessories. The Cellvizio 100 Series is a confocal laser imaging system with a variety of fiber optic probes that is intended to allow confocal laser imaging of the internal microstructure of tissues in anatomical tracts, i.e. gastrointestinal or respiratory, accessed through an endoscope.

**Literature Review**

Fugazza et al. (2016) systematic review is to analyze the current literature on confocal laser endomicroscopy (CLE) and to evaluate the applicability and diagnostic yield of CLE in patients with gastrointestinal and pancreatobiliary diseases. The review included 102 prospective and retrospective clinical studies that evaluated the sensitivity, specificity, or accuracy of CLE. Regarding the use of CLE in biliary duct, it was found that the addition of CLE to histological examination results in a significant increase in diagnostic reliability. Currently, biliary strictures are staged using a combination of endoscopic ultrasound and advanced imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), or EUS, with endoscopic retrograde cholangiopancreatography (ERCP) typically used for tissue sampling, including biopsy and cytological brushing. The current sensitivity of each of these methods is quite low, ranging from 20% to 60%. The present meta-analysis demonstrated that combining CLE with ERCP yields high sensitivity (90%) in the assessment of biliary strictures. The authors conclude that although CLE has several promising applications, its use has been limited by low availability, high cost, and the necessity of specific operator training. The review noted that In order to implement CLE in routine clinical practice there is a need for further clinical trials with a particular focus on cost-effectiveness and medicoeconomic analyses, as well as standardized institutional training.

Meining et al. (2011) reported on a prospective observational multicenter study of 102 patients with indeterminate pancreaticobiliary strictures. Clinical information, ERCP findings, tissue sampling results, and pCLE videos were collected prospectively. A presumptive diagnosis was provided based on probe-based confocal laser endomicroscopy (pCLE) during the procedure before pathology results were available. Patients received at least 30 days of follow-up until definitive diagnosis of malignancy was established or one-year follow-up if index tissue sampling was benign. The main outcome measurements were diagnostic accuracy, sensitivity, specificity of ERCP-guided pCLE compared with ERCP with tissue acquisition. Eighty-nine patients were able to be evaluated with CLE, with 40 patients were proven to have cancer. CLE had a sensitivity of 98% and a specificity of 67% for diagnosing malignancy.

**Professional Societies/Organizations**

**American Society for Gastrointestinal Endoscopy (ASGE):** the ASGE published a technology evaluation status report on confocal laser endomicroscopy (ASGE, 2014). The report notes that on probe-based confocal



laser endomicroscopy (pCLE) allows in vivo real-time visualization of biliary strictures via a dedicated probe passed through a cholangioscope or catheter for ERCP. pCLE can provide real-time microscopic images of the biliary epithelium, thereby providing histological information that is not otherwise available during ERCP.

The report identified several issues pertaining to CLE that deserve further investigation:

- Further studies evaluating the applicability and practicality of CLE, especially in community settings are needed. Although it appears that the current studies of CLE seem promising, these have primarily been in academic centers and their generalizability in nonacademic practices is unknown.
- Additional studies evaluating the learning curve of CLE image interpretation, use of CLE devices, and additional time needed to perform the procedure are needed.
- The clinical efficacy of the technology and its cost-effectiveness compared with other available advanced imaging technologies needs further study.
- Improvements in CLE imaging and image interpretation are needed. Combining CLE imaging with newer molecular markers and the development of computer-based algorithms may be possible avenues for further research in this area.

The report concluded that CLE is an emerging technology that in the bile duct and within pancreatic cysts, it can provide surrogate real-time histological information that has previously been unavailable. The limitations of CLE include the high cost of the equipment and probes, the lack of proven efficacy compared with other widely available advanced imaging techniques, and the need for either intravenous or topical fluorescent contrast agents. The report notes that before the technology can be widely accepted, many further studies are needed to determine its clinical efficacy and evaluate its cost-effectiveness and its utilization in both academic and community settings.

#### **Use Outside of the US**

No relevant information

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#### **Wireless Gastrointestinal Motility Monitoring System (SmartPill®) (CPT Code 91112)**

The SmartPill Gastrointestinal (GI) Monitoring System® (The SmartPill Corporation, Buffalo, NY) has been proposed as an alternative testing method for the diagnosis of gastric conditions and intestinal motility disorders such as gastroparesis and chronic constipation. The system records pH and pressure measurements from the entire length of the gastrointestinal tract for use by physicians to aid in the evaluation of gastrointestinal motility diseases and conditions. Sensors on board an ingestible capsule measure pH and pressure as the capsule travels the length of the GI tract. Measurements are transmitted from the capsule within the GI tract via radiofrequency signal to a patient worn receiver and subsequently downloaded for analysis and review. Next, software performs data analyses providing the physician with a printable report containing regional gut transit times: gastric emptying or transit time (GET), small bowel transit time (SBTT), combined small and large bowel transit time (SLBTT), colonic transit time (CTT) and whole gut transit time (WGTT). The capsule is expelled naturally from the body.

#### **U.S. Food and Drug Administration (FDA)**



The SmartPill GI Monitoring System® was approved in 2006 by the U.S. by the Food and Drug Administration (FDA) under the 510(k) process. Indications for use state SmartPill is used in evaluating patients with suspected gastroparesis. In October 2009, the SmartPill was FDA-approved for the evaluation of colonic transit in patients with chronic constipation, to aid in differentiating slow and normal transit constipation. It is not indicated for use in children.

### **Literature Review**

Hayes (2017) published a directory report for wireless capsule systems for diagnosis of gastroparesis and monitoring of gastrointestinal motility. The review included 13 studies of wireless capsule systems for detection of GI motility disorders that were reported in 14 publications with three cross-sectional comparative studies, seven prospective case-control studies, and three retrospective pretest/posttest studies. Wireless motility capsule (ten studies) or wireless capsule endoscopy (three studies) were compared to reference standards (i.e., gastric scintigraphy, small bowel barium transit, and radiopaque markers). The findings of the report note that although 13 studies were identified that compared wireless capsule systems with other methods for detection of GI motility disorders, these studies provide limited evidence concerning the accuracy of the wireless capsule systems and no reliable evidence that use of these systems improves patient outcomes.

The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review for wireless motility capsule (WMC) versus other diagnostic technologies for evaluating gastroparesis and constipation (Stein, et al., 2013). The review noted WMC appears to be accurate in detection of gastroparesis and slow-transit constipation and may provide increased diagnostic gain as compared with standard motility testing. While the strength of evidence (SOE) is low, the data were relatively consistent and suggested that this modality is no less sensitive than conventional testing. The review noted that the evidence is insufficient to determine whether use of WMC will improve outcomes of care.

Published studies in the peer-reviewed scientific literature are observational or retrospectively conducted with small populations. Although well-established motility testing methods exist, studies are not designed to provide comparison of the accuracy—including sensitivity, specificity, positive and negative predictive values—of the SmartPill to conventional tests as the reference standard in same symptomatic patient population. As a result no strong conclusions can be made regarding the clinical utility of this technology (Kuo, 2011; Rao, 2011a; Camilleri, 2010; Kloetzer, 2010; Sarosiek, 2010; Rao, 2009; Hasler, 2009; Kuo, 2008).

### **Professional Societies/Organizations**

**American College of Gastroenterology (ACG):** The ACG Practice Guideline on Gastroparesis (Camilleri et al. 2013) notes that wireless capsule motility testing is an alternative approach for assessment of gastric emptying; however, further validation is required before it can be considered an alternate to scintigraphy for the diagnosis of gastroparesis. This is noted to be a 'Conditional recommendation, moderate level of evidence'.

**American Gastroenterological Association (AGA):** The AGA Medical Position Statement 'Diagnosis and Treatment of Gastroparesis' (Parkman, et al., 2004) states that GES of a radiolabeled solid meal is the best accepted method to test for delayed gastric emptying. The AGA Medical Position Statement Guidelines on Constipation (AGA, 2013) supports the use of special tests such as CTT, anorectal manometry, balloon-expulsion tests or defecography in refractory patients. Neither guideline addresses the use of SmartPill.

**American and European Neurogastroenterology and Motility Societies:** These organizations published guidelines with consensus recommendations on the indications and optimal methods for the use of transit measurements in clinical practice (Rao, et al., 2011b). The guidelines note that, "The WMC (wireless motility capsule) is a validated and standardized test. It is recommended for assessment of colonic transit time in subjects with constipation and those with suspected colonic disorders. It also provides measurements of regional and whole gut transit."

**American Society of Colon and Rectal Surgeons (ASCRS):** The ASCRS practice parameter for the evaluation and management of constipation notes that anorectal physiology and colon transit time investigations may help to identify the underlying etiology and improve the outcome in patients with refractory constipation. The practice position notes the measurement of colon transit time using radio-opaque markers in patients with suspected slow-transit constipation is inexpensive, simple, and safe (Ternent, et al., 2007).



**North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHN):** The NASPGHN recommendations on evaluation and treatment of constipation in infants and children (2006) notes that an evaluation of colonic transit time with radiopaque markers may be helpful in children with a history of infrequent bowel movements who have no objective findings of constipation.

### Use Outside of the US

National Institute for Health and Care Excellence (NICE): NICE published guidelines regarding assessing motility of the gastrointestinal tract using a wireless capsule. The guidelines note that:

- The evidence on assessing motility of the gastrointestinal tract using a wireless capsule raises no major safety concerns.
- There is evidence of efficacy in measuring gastrointestinal function but uncertainty about the clinical benefit of this, and about patient selection; therefore, this procedure should be used only with special arrangements for clinical governance, consent and audit or research.

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#### **High Resolution Anoscopy (HRA) (CPT Codes 46601, 46607)**

During an anoscopy the perianal area and distal rectum are examined. High resolution anoscopy has been proposed as a method to identify anal lesions in high-risk populations, and for use in screening for anal cytology. High resolution anoscopy uses an anoscope as well as a colonoscope or operating microscope for more detailed examination. After application of a 3% acetic acid solution and Lugol's iodine, the canal is inspected with the colonoscope. Areas with acetowhitening are examined for abnormal patterns and targeted biopsies are performed on areas suspicious for high-grade squamous intraepithelial lesion (HSIL). Correlation of biopsy results with anal cytology results has been variable (Lee, 2010).

#### **Literature Review**

Hayes published a directory report for high-resolution anoscopy (HRA) for the evaluation of anal lesions (2014; 2017). The report concluded that HRA exhibits high sensitivity and moderate specificity for detecting abnormal lesions in high-risk populations. The findings included that HRA is more sensitive than cytology in detecting potentially harmful lesions. There were few studies found that evaluated the capacity of HRA to detect high grade anal intraepithelial neoplasia and findings were too inconsistent to accurately make any determination regarding the validity of HRA for this use.

Randomized controlled clinical trial data are lacking to demonstrate improved health outcomes with the use of high-resolution anoscopy to detect anal cytology. However, there is support by a number of professional societies/organizations related to its use as diagnostic tool in individuals with a suspicious anal lesion, including high-grade suspicious intraepithelial lesion (HSIL) and anal dysplasia found in prior cytology/biopsy.

A case series by Chang (2002) reported on a prospective study of high resolution anoscopy directed surgery in 37 patients with high-grade squamous intraepithelial lesion. Twenty-nine patients tested positive for human



immunodeficiency virus (HIV), eight patients tested negative. Mean follow-up was 32.3 months for HIV-positive patients and 28.6 months in HIV-negative patients. No HIV-negative patient developed recurrent high-grade squamous intraepithelial lesions. Twenty-three of 29 HIV positive patients had persistent or recurrent high-grade squamous intraepithelial lesions (HSIL) ( $p < .003$ ). Six patients underwent reoperation for HSIL; four recurred by six months. No patients developed incontinence, stenosis, postoperative infection, or significant bleeding after surgical treatment. Study limitations include small patient population and uncontrolled study design.

#### **Professional Societies/Organizations**

**American Society of Colon and Rectal Surgeons (ACRS):** The ACRS (Steele, et al., 2012) published practice parameters for anal squamous neoplasms. The guideline notes that targeted destruction guided by high resolution anoscopy is effective to identify, biopsy, and destroy low grade anal intraepithelial neoplasm [LGAIN]/high grade anal epithelial neoplasm [HGAIN] without the morbidity associated with wide local excision. The Guidelines also note that a comprehensive approach with cytology, high resolution anoscopy, targeted biopsies, and directed therapy has reported clearance of high grade anal intraepithelial neoplasm [HGAIN] in up to 80%, with progression to higher-grade disease and invasive cancer in less than 5%. Therefore, expectant management with close follow-up may be considered in select cases depending on risk factors, comorbidities, and available resources. However, because of the high prevalence of concomitant cervical intraepithelial neoplasm, a referral to gynecology is recommended to complete the evaluation. Targeted destruction and close clinical long-term follow-up is appropriate therapy for LGAIN/HGAIN. (Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C)

#### **Use Outside of the US**

**Ontario Health Technology Assessment Series (OHTAS):** OHTAS (2007) notes that high resolution anoscopy rather than routine anoscopy-guided biopsy is considered to be the diagnostic standard.

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#### **13C-Spirulina Gastric Emptying Breath Test (GEBT) (CPT code 91299)**

Gastroparesis is a syndrome of objectively delayed gastric emptying in the absence of a mechanical obstruction and cardinal symptoms of nausea, vomiting, early satiety, bloating, and/or upper abdominal pain. In patients with suspected gastroparesis and no evidence of a mechanical obstruction on imaging or upper endoscopy, an assessment of gastric motility is necessary to establish the diagnosis of gastroparesis. Delayed gastric emptying on scintigraphy is required to establish the diagnosis of gastroparesis (Camilleri, [UpToDate], 2016). A more recently developed test, the 13C-Spirulina Gastric Emptying Breath Test (GEBT) (Cairn Diagnostics, Brentwood, TN) has been proposed as an alternative approach for the assessment of gastric emptying. While this test has the advantage of avoiding radiation associated with scintigraphy, further studies are needed before they can be routinely recommended for evaluation of delayed gastric emptying (Camilleri, [UpToDate], 2016).



A kit containing the specially labeled test meal and all components necessary to administer the test meal and collect breath samples is provided to the test administration site by Cairn Diagnostics. The collected breath samples are returned to Cairn's CLIA-certified clinical laboratory for analysis by gas isotope ratio mass spectrometry (GIRMS). The patient will eat a special test meal, and then additional breath samples are collected at specified times. Once the test meal is consumed, the carbon-13 in the Cairn GEBT test meal gives rise to carbon-13 labeled CO<sub>2</sub>, or <sup>13</sup>CO<sub>2</sub>, which can be measured in the breath samples.

### **Literature Review**

Szarka conducted a study to validate <sup>13</sup>C-Spirulina platensis gastric emptying (GE) breath test (GEBT) with a standardized meal. The study included 38 healthy volunteers and 129 patients with clinically suspected delayed gastric emptying (GE) who underwent measurements at 45, 90, 120, 150, 180, and 240 minutes after a 238 kcal meal labeled test with 100 mg [<sup>13</sup>C]-S platensis and 0.5 mCi <sup>99m</sup>Tc. The authors established normal ranges for scintigraphy with the test meal, intra-individual and inter-individual coefficients of variation (COVs), and the ability of the GEBT breath percent dose excreted \*1000 values to predict scintigraphic half-life and to categorize GE as delayed, normal, or accelerated. In healthy group, the 10th and 90th percentiles of half-life for scintigraphic GE with this meal were 52 and 86 minutes; intra-individual COVs for scintigraphy and the GEBT were, respectively, 31% and 27% at 45 minutes, 17% and 21% at 90 minutes, 13% and 16% at 120 minutes, 10% and 13% at 150 minutes, and 8% and 12% at 180 minutes. The inter-individual COVs at each time for the [<sup>13</sup>C] GEBT and scintigraphy were typically approximately 1%-4% lower than intra-individual COVs. Individual breath samples at 45, 150, and 180 minutes predicted GE category; at 80% specificity, 45- and 180-minute samples combined were 93% sensitive to identify accelerated GE, and 150- and 180-minute combined were 89% sensitive for delayed GE.

### **U.S. Food and Drug Administration (FDA)**

<sup>13</sup>C-Spirulina Platensis Gastric Emptying Breath Test (Gastric Emptying Breath Test, [GEBT]) (Advanced Breath Diagnostics LLC, Brentwood TN) received premarket approval (PMA) April 2015. The Gastric Emptying Breath Test (GEBT), to be used with the GEBT test meal, is intended for use in the measurement of the rate of gastric emptying of solids and as an aid in the diagnosis of delayed gastric emptying (gastroparesis) in adult humans who are symptomatic for gastroparesis.

Contraindications include:

- Individuals with known hypersensitivity to Spirulina, egg, milk or wheat allergens should avoid the GEBT.
- Because the GEBT is an indirect multi-compartmental method of measuring gastric emptying, GEBT results may be inaccurate in individuals compromised with significant small bowel, pancreatic, liver and/or lung disease. Consequently GEBT should not be administered to patients with pulmonary dysfunction (e.g. COPD) and/or small bowel malabsorption.

Approval was based on the observation in a study of 115 patients who underwent simultaneous scintigraphy and spirulina <sup>13</sup>C breath test. At 80 percent specificity, the <sup>13</sup>C-spirulina breath test samples at 150 and 180 minutes had a combined sensitivity of 89 percent for delayed gastric emptying.

### **Professional Societies/Organizations**

**American College of Gastroenterology (ACG):** ACG published clinical guidelines for management of gastroparesis. The recommendations include, "Alternative approaches for assessment of gastric emptying include wireless capsule motility testing and <sup>13</sup>C breath testing using octanoate or spirulina incorporated into a solid meal; they require further validation before they can be considered as alternates to scintigraphy for the diagnosis of gastroparesis. (Conditional recommendation, moderate level of evidence)"

### **Use Outside of the US**

No relevant information

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## **Coding/Billing Information Gastroenterology**

**Note:** 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

### **Anoscopy, High Resolution (HRA)**

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

<b>CPT®* Codes</b>	<b>Description</b>
<a href="#">46601</a>	Anoscopy; diagnostic, with high-resolution magnification (HRA) (eg, colposcope, operating microscope) and chemical agent enhancement, including collection of specimen(s) by brushing or washing, when performed
<a href="#">46607</a>	Anoscopy; with high-resolution magnification (HRA) (eg, colposcope, operating microscope) and chemical agent enhancement, with biopsy, single or multiple

### **Additional Services Considered Experimental/Investigational/Unproven:**

<b>CPT®* Codes</b>	<b>Description</b>	<b>Comment</b>
<a href="#">46999</a>	Unlisted procedure, anus	Considered Experimental/Investigational/Unproven when used to report transanal radiofrequency therapy for fecal incontinence (e.g., SECCA procedure)
<a href="#">83993</a>	Calprotectin, fecal	
<a href="#">91112</a>	Gastrointestinal transit and pressure measurement, stomach through colon, wireless capsule, with interpretation and report	
<a href="#">91299</a>	Unlisted diagnostic gastroenterology procedure	Considered Experimental/Investigational/Unproven when used to report 13C-Spirulina Gastric Emptying Breath Test



		(GEBT)
<a href="#">0397T</a>	Endoscopic retrograde cholangiopancreatography (ERCP), with optical endomicroscopy (List separately in addition to code for primary procedure)	

\*Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.

## **Neurology**

### **Quantitative Sensory Testing (QST) (CPT Codes 0106T, 0107T, 0108T, 0109T, 0110T; HCPCS Code G0255)**

QST is a psychophysical test used to assess and quantify small and large-fiber sensory nerve function by the use of touch, thermal (i.e., hot and cold), pain, and/or vibratory sensations. QST, a noninvasive study, is proposed to be able to detect early, subtle changes in small and large sensory nerve fibers. It has been proposed as a complementary diagnostic and monitoring tool to be used with traditional testing (e.g., Semmes-Weinstein monofilaments, Rydel Seiffert graduated tuning fork) for the detection of sensory nerve abnormalities for conditions such as diabetic neuropathy, carpal tunnel syndrome, multiple sclerosis and vitamin B deficiencies. QST has also been proposed for multiple other indications including: identifying HIV-associated peripheral neuropathy, use before and after lumbar discectomy to analyze sensory nerve dysfunction in the lower-extremities, following greater saphenous vein stripping to evaluate postoperative sensory changes, and prior to and following spinal cord stimulation for patients with chronic neuropathic pain due to either failed back surgery syndrome or complex regional pain syndrome, evaluation of sexual dysfunction, peripheral nerve dysfunction, painful bladder syndrome, and radiculopathy.

Several limitations of QST have been documented including a potential for bias if the patient is cognitively impaired or desires an abnormal result. QST has no localizing value because it is reflective of the integrity of the entire sensory neuraxis from receptors to brain. Abnormal QST values may occur because of peripheral nerve or central nervous system dysfunction. The test may lack objectivity due to patient status (e.g., distraction, boredom, inattention, fatigue, drowsiness), which may be enhanced by the time it takes to complete the test (e.g., one to two hours). The inclusion of the patient's reaction time to a stimulus may distort the actual sensory threshold. Electrode size, site of stimulation, method and rate of change of the stimulation, method of obtaining patient's response, and variations in testing devices make reproducibility of the test results difficult. There is also a lack of standardization for testing procedures and reporting outcomes, therefore test execution may differ with different examiners. Due to these variables, it is proposed that quantitative sensory testing (QST) lacks the objectivity of conventional nerve conduction studies (Pavlovic, et al., 2010; Backonja, et al., 2009; Siemionow, et al., 2006; Chong, et al., 2004; Shy, et al., 2003).

The various testing methods and devices used for QST to determine sensory abnormalities include:

- Electrical current testing such as current perception threshold testing or sensory nerve conduction testing (sNCT) which assesses sensory function. Examples of these devices include the Medi-DX 7000 (Neuro-Diagnostic Associates, Laguna Beach, CA) and the Neurometer® CPT or s-NCT (Neurotron, Inc., Baltimore, MD).
- Pressure-specified sensory testing evaluates nerve function by detection of light, status, and moving touch. Devices include the NK Pressure-Specified Sensory Device™ (PSSD) (NK Biotechnical Engineering Co., Minneapolis, MN).
- Thermal testing is used to assess a distinction between predominantly C fiber and A-delta fiber activity by the application of cold and heat. Examples of thermal devices by Medoc Advanced Medical Systems LTD (Minneapolis, MN) include the Contact Heat-Evoked Potential Stimulator (CHEPS), GSA Genito, TSA-2001 Sensory Analyzer, and the TSA-2001 Sensory Analyzer.
- Vibration perception threshold testing, or vibratory testing, assesses large myelinated nerve fiber dysfunction and measures sensory thresholds. The VSA-3000 Vibratory Sensory Analyzer (Medoc Advanced Medical Systems, Eilat, Israel) and the Bio-thesiometer (Bio-Medical Instruments, Newbury, OH) are examples of these devices.



- Voltage-actuated sensory nerve conduction threshold (V-sNCT) testing is used to evaluate the sensitivity, specificity and predictive value of A-delta fibers to assess localized pain sources. These devices include the Neural-Scan (Neuro-Diagnostic Associates [NDA], Inc., Laguna Beach, CA).
- Pain-fiber nerve conduction testing (pf NCV), also referred to as pain fiber nerve testing, has been proposed as a method of evaluating the severity, location and distribution of pain associated with conditions such as radiculopathy and/or neuropathy. According to the American Association of Sensory Electrodiagnostic Medicine (AASEM, 2015), this type of nerve testing is noninvasive, employs the use of a device, such as the Axon II, Neural Scan, and is conducted using a voltage actuated stimulus (sensory nerve conduction) and a potentiometer to measure the amplitude of the action potential.

**U.S. Food and Drug Administration (FDA):** QST systems and devices are approved by the FDA 510(k) process and are classified either as a Class II device or an unclassified device.

### Literature Review

Hayes published a technology directory report regarding quantitative sensory testing for the diagnosis of lower extremity peripheral neuropathy (Hayes 2014; 2017). The review included 29 prospective or retrospective cohort, cross-sectional, matched-group, or case-control studies that evaluated QST for detection of neuropathy or foot ulcer and/or amputation susceptibility. There were no studies identified that relied on QST to guide patient management. Findings of the report noted that all of the available studies of QST are of poor to very poor quality and the amount and consistency of evidence concerning QST for the diagnosis of neuropathy varies widely, depending on the type of QST and the indication for testing. Some evidence suggests that vibration QST has moderate to high accuracy for the diagnosis of neuropathy and that monofilament QST and vibration QST have moderate to high accuracy for the diagnosis of loss of protective sensation as reflected in susceptibility to foot ulcer and/or amputation as a consequence of neuropathy. It was noted that there is insufficient evidence to evaluate monofilament QST for the diagnosis of neuropathy or to evaluate thermal QST, ball bearing QST, 2-point discrimination QST, or tactile circumferential QST for the diagnosis of neuropathy or susceptibility to foot ulcer and/or amputation. The report concluded that the best available studies do not provide consistent evidence that quantitative sensory testing (QST) has high accuracy for the diagnosis of neuropathy or loss of protective sensation.

The clinical significance of QST has not been demonstrated in clinical trials (Atherton, et al., 2007; Soomekh, et al., 2006; Chong, et al., 2004; Shy, et al., 2003). Additionally, evidence in the published peer-reviewed scientific literature does not support the clinical utility of QST. Randomized controlled clinical trial data are scarce; studies are primarily in the form of nonrandomized comparative studies and case series with heterogeneous small patient populations, using a variety of different devices. QST has not been recommended as a stand alone test. Limitations of the studies include: weak study methodology; inability to verify data; lack of a control group; numbers of patients lost to follow-up; numbers of patients who did not complete all of the testing; lack of comparisons to conventional neurological tools; variations in testing parameters, equipment and protocol; and lack of randomization (Eisenberg, et al., 2006; England, et al., 2005/2008; Centers for Medicare and Medicaid Services, 2003).

### Professional Societies/Organizations

**American Academy of Orthopedic Surgeons (AAOS):** In their guidelines on the diagnosis of carpal tunnel syndrome, AAOS (2007) noted that the physician should not routinely evaluate patients with suspected carpal tunnel syndrome with new technology such as pressure specified sensorimotor devices.

**American Academy of Neurology (AAN):** In a report on QST based on a review of 350 articles, the AAN (Shy, et al., 2003; reaffirmed 2008 and 2013) noted QST is a potentially useful tool for measuring sensory impairment for clinical and research studies. However, QST results should not be the sole criteria used to diagnose pathology". The AAN indicated that malingering and other nonorganic factors can affect the outcomes of the test results. They also noted that well-designed studies to compare the various types of QST devices and methodologies are indicated and should include patients with abnormalities detected solely by QST.

In a report on distal symmetric polyneuropathy (England, et al., 2005; reaffirmed 2008), the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation stated that QST was not recommended as a diagnostic tool because the sensitivities



and specificities varied widely among the studies, and the tests have inherent variability. QST is difficult to standardize, and reproducibility of results ranged from poor to excellent.

**American Association of Electrodiagnostic Medicine (AAEM):** The AAEM (Chong, et al., 2004) conducted a review of the literature on QST to assess the “methodology, reliability, reproducibility, limitations, and potential clinical applications” of these studies. The authors noted the following conclusions:

- QST is a reliable psychophysical test of large- and small-fiber sensory modalities.
- QST tests the integrity of the entire sensory axis from receptors to brain. Abnormalities do not localize dysfunction to the central or peripheral nervous system, or any particular location along the peripheral nervous system.
- QST is highly dependent on the full cooperation of the patient and may be falsely abnormal if the patient is biased toward an abnormal result or is cognitively impaired. No algorithm can reliably distinguish between psychogenic and organic abnormality.
- QST has been shown to be reasonably reproducible over a period of days or weeks in normal subjects. Since longitudinal QST studies of patients in drug trials are usually done over a period of several months to a few years, reproducibility studies on the placebo-controlled group should be included.
- The reproducibility of thermal thresholds may not be as good as that of vibration threshold.
- For individual patients, more studies are needed to determine the maximum allowable difference between two QSTs that can be attributed to experimental error.
- Different commercially available QST instruments have different specifications (thermode size, stimulus characteristics), testing protocols, algorithms, and normal values. Only QST instruments and their corresponding methodologies that have been shown to be reproducible should be used for research and patient care.
- The results of QST can only be interpreted properly if machine calibration and testing protocol are strictly followed.
- The literature does not allow a conclusion to be made regarding whether any QST instrument is better than another.

#### **Use Outside of the US**

**European Federation Of Neurological Societies (EFNS):** In their 2009 guidelines (Cruccu, 2009) on the assessment of neuropathic pain, EFNS stated that studies using qualitative sensory testing (QST) lack blinding, involve a broad spectrum of patients and controls, and only four of 50 new studies were prospective. The variability of methods, results, and patient populations (e.g., diabetic neuropathy, spinal cord injury, radiculopathy) prevent any conclusions from being drawn. The Society stated that qualitative sensory testing (QST) may be used to document the sensory profile, but the test “cannot be considered sufficient to separate differential diagnoses”. “Quantitative sensory testing (QST) is helpful to quantify the effects of treatments on allodynia and hyperalgesia and may reveal a differential efficacy of treatments on different pain components”. They “do not recommend the systematic measure of thermal stimuli except for pathophysiological research or treatment trials. A simple and sensitive tool to quantify pain induced by thermal stimuli in clinical practice is still lacking”.

**International Association for the Study of Pain (IASP®):** In guidelines on neuropathic pain assessment (Haanpää, 2011), the Special Interest Group on Neuropathic Pain of the IASP (NeuPSIG) explains that QST is biased towards thermal, including nociceptive, testing, which means that it excludes assessment of large fiber function. According to NeuPSIG, more studies with complete somatosensory profiles are needed. Results of available studies have been inconsistent and conflicting. Since QST abnormalities are found in non-neuropathic pains, these tests cannot be taken as a conclusive demonstration of neuropathic pain. Further, NeuPSIG notes QST can be used in clinic along with bedside testing, but it cannot allow for estimation of the level of the lesion within the neuraxis. The relevance of QST to predict therapeutic outcome has yet to be established in prospective studies.

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### **Physiologic Recording of Tremor Using Accelerometer/Gyroscope (CPT Code 95999)**

Accelerometers and gyroscopes are devices that may be used to objectively record and monitor motion and electrical activity of muscles to measure tremor in individuals with movement disorders. Recent studies have examined the clinical utility of these devices as an adjunct in diagnosis and measurement of functional ability and recovery in individuals with dyskenetic disorders.

### **U.S. Food and Drug Administration (FDA)**

The FDA approved the Kinesia™ device (Cleveland Medical Service, Cleveland, OH) in April 2007 for the monitoring and recording of motion and electrical activity of muscle to quantify kinematics of movement disorders such as tremor for research and diagnostic purposes. The Tremorometer® (FlexAble Systems, Inc., Fountain Hills, AZ) received substantial equivalency FDA 510 (k) approval in January 2001. It is a system designed to improve the measurement and quantification of tremor in human patients regardless of the etiology.

### **Literature Review**

Controlled clinical trial data are lacking to inform the utility of these devices, including the translation of measurements into meaningful outcomes. Cheung et al. (2011) performed a systematic literature review; reviewing 54 studies that used accelerometers to classify human movement and to appraise their potential to determine the level of activity of older persons in hospital settings. Outcome measures criteria were comparisons of derived classifications of postural movements and mobility against those made by using observations. A number of limitations to the study were noted including the number and type of accelerometers used for measurement, varied age of study participants (varied from teenager to >60 yrs). Most studies were limited by small sample size; 54% had 10 subjects or less. Methods for validating data were also varied. Of the accelerometer studies included in this review, only 17 were conducted on patients and the remaining were conducted on healthy subjects (n=37 studies). The authors note that the literature review indicates that only a limited number of studies have applied accelerometry to measure activities in patients, of which six studies were of older patients. These studies were limited by smaller sample sizes and use of multiple accelerometer devices attached to different body positions. The activity classification algorithms validated in small sample size studies with <6 patients are insufficient for clinical use. A suitable algorithm for application in geriatric rehabilitation settings needs to be generic and accurate in older patients with different levels of mobility impairment.

Gebruers et al. (2010) reported results of a systematic review assessing the clinical applicability of different accelerometry based measurement techniques in persons with stroke. Twenty-five articles were selected for inclusion; there were 4 randomized controlled trials (RCT). The authors noted that although the available evidence may suggest that accelerometers yield valid and reliable data about individuals with stroke, data are young, limiting the ability to draw consistent conclusions. Further research is necessary to investigate predictive value and responsiveness.

### **Use Outside of the US**

No relevant information.

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### **Adrenal and Fetal Mesencephalic Transplantation for Parkinson Disease (HCPCS Code S2103)**

There are scarce data in the published, peer-reviewed scientific literature regarding the current clinical use of adrenal-to-brain transplantation in humans for any indication. In a systematic review of the literature, the Agency for Healthcare Research and Quality ([AHRQ], 2003) noted that there is a lack of efficacy and substantial morbidity associated with the procedure for the treatment of Parkinson disease (PD). The AHRQ also concluded that adrenal medullary transplants are no longer performed to treat PD.

There is ongoing research in animal and human models relative to the use of fetal mesencephalic transplantation as a replacement source of dopamine-producing cells. In this procedure, fetal brain cells (i.e., neurons) that produce dopamine are implanted in the putamen or head of the caudate area of the brain, which is the area controlling movement. In theory, the transplanted neurons can replace the loss of normal dopamine-producing cells. These fetal cells may be human or xenogeneic (i.e., derived from a different species).

Clinical improvement was demonstrated in small numbers of individuals with PD undergoing transplantation of fetal tissue in several nonrandomized studies; however, results have not been replicated in double-blind sham-surgery controlled clinical trials (Olanow, 2003; Freed, 2001). Transplantation of fetal substantia nigra into the stratum has failed to show significant efficacy and has been associated with the side effect of transplant-induced off-medication dyskinesias. More recently, implanted dopamine neurons have been found to contain Lewy bodies, suggesting that they are dysfunctional and may have been affected by the PD pathological process (Olanow, 2009).

The data is scarce regarding the safety and effectiveness of xenogeneic fetal cells for any indication in humans. Schumacher et al. (2000) reported results of a case series study of 12 individuals with Parkinson disease who underwent unilateral implantation of embryonic porcine ventral mesencephalic tissue (Schumacher, 2000). In the medication-off state, total Unified Parkinson's Disease Rating Scale scores improved by 19% ( $p=.01$ ). At the time of study publication there were no reported permanent complications. Limitations of the study include small size, uncontrolled study design, and short-term follow-up.

### **U.S. Food and Drug Administration (FDA)**

The FDA Center for Biologics and Research regulates the transplantation of fetal/embryonic cells. Companies supplying cell and tissue-based products must register and list their products with the FDA.

### **Professional Societies/Organizations**

**American Academy of Neurology (AAN):** The AAN in an evaluation of surgery for Parkinson's disease (Hallett, et al., 1999) recommended that adrenal-to-brain transplantation not be performed because of unacceptable risk to the patient. They further noted that the procedure was no longer being studied. Regarding fetal mesencephalic transplantation the AAN notes that, while the procedure is promising, it remains experimental due to lack of controlled clinical trials. The authors determined that there were small, nonrandomized case studies which noted functional improvement in some patients; however, unacceptably high levels of morbidity and mortality were associated with the procedure. Review of pathologic reports found that few transplanted cells survived long term, suggesting that benefit of the procedure would be of short duration.

The authors also reviewed the documented studies of fetal mesencephalic transplantation. Studies were small and nonrandomized. There was variation between the studies in the techniques utilized, the site of transplantation, the number of mesencephalons used, and the immune-suppressive regimen provided. In all of the studies some of the patients demonstrated improvement in motor function. The summary notes that while the



procedure is promising because it appears effective and has low morbidity and mortality, it is considered experimental because of the absence of controlled studies.

### **Use Outside of the US**

No relevant information

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### **Whole Body and Select Head Hypothermia in the Neonate (CPT Code 99184)**

Hypoxic ischemic encephalopathy is characterized by the need for resuscitation at birth, neurologic depression, seizures, and electroencephalographic abnormalities. No specific clinical intervention has been shown to alter outcome. Total body and selective head hypothermia (e.g., a reduction in brain temperature of two-five degrees) in the neonatal population have been proposed as a therapeutic intervention to reduce death as well as neurodevelopmental disabilities.

According to Gluckman et al. (2005) the neuroprotective effects of experimental cooling are dependent on both a sufficient duration of cooling and on the timing of initiation of cooling. Extended cooling for 24–72 hours, started as late as six hours after injury, has been associated with persistent protection.

### **Literature Review**

Jacobs et al. (2013) reported on a Cochrane review regarding cooling for newborns with hypoxic ischemic encephalopathy to determine the effect of therapeutic hypothermia in encephalopathic asphyxiated newborn infants on mortality, long-term neurodevelopmental disability and clinically important side effects. The review included 11 randomized, controlled studies (=1505) with term and late preterm infants with moderate/severe encephalopathy and evidence of intrapartum asphyxia that compared the use of therapeutic hypothermia with standard care. The authors concluded that there is evidence from the trials included in the systematic review that therapeutic hypothermia is beneficial in term and late preterm newborns with hypoxic ischemic encephalopathy. They noted that cooling reduces mortality without increasing major disability in survivors. The benefits of cooling on survival and neurodevelopment outweigh the short-term adverse effects. The authors note that hypothermia should be instituted in term and late preterm infants with moderate-to-severe hypoxic ischemic encephalopathy if identified before six hours of age.



Shankaran et al (2005) reported results of a randomized controlled clinical trial of hypothermia in infants with a gestational age of at least 36 weeks who were admitted to the hospital at, or before six hours of age with either severe acidosis or peri-natal complications and resuscitation at birth. The infants had moderate or severe encephalopathy. Study participants were randomly assigned to standard care (control, n=106) or whole body cooling (i.e., esophageal temperature of 33.5 degrees Celsius for 72 hours, followed by slow re-warming, hypothermia group, n=102). Neurodevelopmental outcome was assessed at 18 to 22 months of age. The primary outcome was death or severe disability. Death or moderate or severe disability occurred in 44 % in the hypothermia group and 62 % of infants in the control group ( $p = 0.01$ ). Twenty-four and 38 infants died in the hypothermia and control groups, respectively, ( $p = 0.08$ ). The rate of cerebral palsy was 19% and 30% in the hypothermia and control groups, respectively ( $p = 0.20$ ). Data suggest that whole-body hypothermia reduces the risk of death or disability in this patient population.

In a follow-up to this study Shankaran et al. (2012) reported long-term outcomes of evaluable study participants. Of the 208 trial participants, primary outcome data were available for 190. Of the 97 children in the hypothermia group and the 93 children in the control group, death or an intelligence quotient (IQ) score below 70 occurred in 46 and 58, respectively ( $p=0.06$ ). In these same groups, death occurred in 27 and 41, respectively, in the hypothermia and control groups ( $p=0.04$ ). Death or severe disability occurred in 38 and 53, respectively, in the hypothermia and control groups ( $p=0.03$ ). The rate of the combined end point of death or an IQ score of less than 70 at six to seven years of age was lower among children undergoing whole-body hypothermia than among those undergoing usual care. Outcomes were not statistically significant. Data suggest that hypothermia results in lower death rates; the rates of severe disability among survivors did not increase in the group undergoing hypothermia.

Azzopardi et al. (2009) performed a randomized controlled study of infants who were less than six hours of age and had a gestational age of at least 36 weeks and peri-natal encephalopathy. The study compared outcomes for infants receiving intensive care plus whole body hypothermia 33.5 degrees Celsius for 72 hours (n=163) with intensive care alone (n=162). The primary outcome was death or severe disability at 18 months of age. In the group undergoing hypothermia 42 infants died; 32 infants survived but had severe neurodevelopmental disability. In the intensive care treatment arm 44 infants died and 42 had severe disability ( $p = 0.17$ ). Infants in the cooled group had an increased survival without neurological abnormality ( $p = 0.003$ ). Among survivors, cooling resulted in reduced risks of cerebral palsy ( $p = 0.03$ ) and improved scores on the Mental Developmental and Psychomotor Developmental Indexes of the Bayley Scales of Infant Development II ( $p = 0.03$  for each) and the Gross Motor Function Classification System ( $p = 0.01$ ). Data suggest that moderate hypothermia for 72 hours did not significantly reduce the combined rate of death or severe disability but resulted in improved neurological outcomes in survivors who received hypothermia.

In a multi-center randomized controlled trial Zhou et al (2010) examined the safety and the effectiveness of selective head cooling (SHC) with mild systemic hypothermia (i.e., nasopharyngeal temperature of 34 $\pm$ 0.2 C and rectal temperature of 34.5-35.0 Celsius for 72 hours) in infants with hypoxic ischemic encephalopathy (HIE). Infants were randomly assigned to the SHC or the control group. SHC was initiated within six hours after birth for infants in the hypothermia group. Rectal temperature was maintained at 36.0 to 37.5 degrees Celsius in the control group. Neurodevelopmental outcome was assessed at 18 months of age. The primary outcome was a combined end point of death and severe disability. The combined outcome of death and severe disability, mortality rate, and severe disability rates were significant ( $p = 0.01$ ;  $p = 0.16$ ; and  $p = 0.01$ ) for the SHC and control groups, respectively. Data suggest that SHC with mild systemic hypothermia may significantly decrease the combined outcome of severe disability and death, as well as severe disability.

### **Professional Societies/Organizations**

**American Heart Association (AHA):** In a special report, the AHA published Neonatal Resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Kattwinkel, et al., 2010). Regarding therapeutic induced hypothermia the AHA recommendation notes that infants born at  $\geq 36$  weeks gestation with evolving moderate to severe hypoxic ischemic encephalopathy should be offered therapeutic hypothermia. The treatment should be implemented according to the studied protocols, which currently include commencement within six hours following birth, continuation for 72 hours, and slow rewarming over at least four hours. Further, therapeutic hypothermia should be administered under clearly



defined protocols similar to those used in published clinical trials and in facilities with the capabilities for multidisciplinary care and longitudinal follow-up.

#### **Use Outside of the US**

No relevant information

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#### **Percutaneous or Open Implantation of Electrode Array (CPT codes 64999)**

Percutaneous or open implantation of a neurostimulator electrode array is a technique being investigated for treatment of chronic pain where stimulation is delivered by a pulse generator and an electrode that is placed subcutaneously at the site of maximum pain rather than at the site of the nerve. This technique also referred to as subcutaneous target stimulation (STS) or peripheral nerve field stimulation (PNFS) involves a temporary trial period in which an electrode is placed subcutaneously by open or percutaneous approach, is secured in place with suture, and is then attached to a generator for approximately two to 14 days. A trial is considered successful if there is at least 50% pain reduction. Following a successful temporary trial the device is implanted

**U.S. Food and Drug Administration (FDA):** FDA approval for specific PNFS devices was not found on the FDA site. However, PNFS can be carried out using leads and electrodes that are primarily designed for spinal cord stimulation and may be considered an off-label use of these devices.

#### **Literature Review**

Randomized controlled clinical trial data, and meta-analyses are lacking in the published, peer-reviewed scientific literature and there is insufficient evidence to determine safety and effectiveness of this therapy. Published peer-reviewed clinical trial data is primarily limited to case series and retrospective reviews.

#### **Use outside of the US**

The National Institute for Health and Care Excellence (UK, [NICE], 2013) published guidance regarding peripheral field nerve stimulation for chronic low back pain. NICE recommendations note that evidence on efficacy is very limited, in both quality and quantity. Likewise, evidence on safety is also limited and there is a risk of complications from any implanted device. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

#### **References**

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### **External Heart Rate and 3-Axis Accelerometer Monitoring to Diagnose Nocturnal Epilepsy (CPT Codes 0381T, 0382T, 0383T, 0384T, 0385T, 0386T)**

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures (Abou-Khalil, 2012). Standard evaluation and diagnosis of seizures and epilepsy includes an in-depth clinical history; an electroencephalogram and other brain imaging may be used to supplement the history, help classify the type of seizure and determine underlying pathology. A number of epileptic seizure syndromes exist including several which are characterized by the occurrence of seizures at night, while the individual is sleeping and unattended. Nocturnal seizures often occur in children. Use of external heart rate and 3-axis accelerometer monitoring has been proposed as a method to detect/diagnose nocturnal epilepsy. Three-axial accelerometer measures the movement (acceleration) in three orthogonal directions fixed to a sensor by way of soft bands generally affixed to the wrists and/or ankles.

### **Literature Review**

Published, peer-reviewed data are limited regarding the effectiveness of accelerometer monitoring to diagnose epilepsy, including nocturnal epilepsy (Beniczky, 2013; Van de Vel, 2013). Studies are limited by uncontrolled design, small participant numbers and short-term follow-up.

Beniczky et al. (2013) reported outcomes of a prospective study designed to assess the clinical reliability of a wrist-worn, wireless accelerometer sensor for detecting generalized tonic-clonic seizures in 73 consecutive patients. The wireless wrist accelerometer correctly detected 35 seizures (89.7%). The mean sensitivity per patient (with seizure) was 91%. Twenty-eight seizures occurred during sleep and eleven seizures occurred when the patient was awake. The device had a similar accuracy for detecting nocturnal and daytime seizures. One hundred forty-nine seizures other than generalized tonic-clonic seizures were recorded (simple partial, 37; complex partial/psychomotor, 31; focal tonic, 6; hypermotor, 6; absence, 1; myoclonus, 60; psychogenic nonepileptic seizure, 8). Study limitations include uncontrolled design, small study numbers and short-term follow-up.

### **Use Outside of the US**

No relevant information

### **References**

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### **Coding/Billing Information Neurology**

**Note:** 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

### **Whole Body or Selective Head Therapeutic Hypothermia**

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

<b>CPT®* Codes</b>	<b>Description</b>
<a href="#"><u>99184</u></a>	Initiation of selective head or total body hypothermia in the critically ill neonate, includes appropriate patient selection by review of clinical, imaging and laboratory data, confirmation of esophageal temperature probe location, evaluation of amplitude EEG, supervision of controlled hypothermia, and assessment of patient tolerance of cooling



**Neurology Services Considered Experimental/Investigational/Unproven:**

<b>CPT® Codes</b>	<b>Description</b>	<b>Comment</b>
<a href="#">64999</a>	Unlisted procedure, nervous system	Considered Experimental/Investigational/Unproven when used to report implantation of trial or permanent electrode arrays or pulse generators for peripheral subcutaneous field stimulation
<a href="#">95999</a>	Unlisted neurological or neuromuscular diagnostic procedure	Considered Experimental/Investigational/Unproven when used to report tremor measurement with accelerometer(s) and/or gyroscope(s)
<a href="#">0106T</a>	Quantitative sensory testing (QST), testing and interpretation per extremity; using touch pressure stimuli to assess large diameter sensation	
<a href="#">0107T</a>	Quantitative sensory testing (QST), testing and interpretation per extremity; using vibration stimuli to assess large diameter fiber sensation	
<a href="#">0108T</a>	Quantitative sensory testing (QST), testing and interpretation per extremity; using cooling stimuli to assess small nerve fiber sensation and hyperalgesia	
<a href="#">0109T</a>	Quantitative sensory testing (QST), testing and interpretation per extremity; using heat-pain stimuli to assess small nerve fiber sensation and hyperalgesia	
<a href="#">0110T</a>	Quantitative sensory testing (QST), testing and interpretation per extremity; using other stimuli to assess sensation	
<a href="#">0381T</a>	External heart rate and 3-axis accelerometer data recording up to 14 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional	
<a href="#">0382T</a>	External heart rate and 3-axis accelerometer data recording up to 14 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only	
<a href="#">0383T</a>	External heart rate and 3-axis accelerometer data recording from 15 to 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional	
<a href="#">0384T</a>	External heart rate and 3-axis accelerometer data recording from 15 to 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only	
<a href="#">0385T</a>	External heart rate and 3-axis accelerometer data recording	



	more than 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional	
<a href="#">0386T</a>	External heart rate and 3-axis accelerometer data recording more than 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only	

HCCPS Codes	Description
<a href="#">G0255</a>	Current perception threshold/sensory nerve conduction test, (sNCT) per limb, any nerve
<a href="#">S2103</a>	Adrenal tissue transplant to brain

\*Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.

## **Obstetrics/Gynecology**

### **Laparoscopic Radiofrequency Ablation (RFA) of Uterine Fibroids (CPT codes 58674)**

Laparoscopic RFA has been proposed for the treatment of uterine fibroids of all sizes. In this minimally invasive procedure a laparoscopic ultrasound probe is used to determine the location and size of fibroids. An electrode array delivers alternating radiofrequency energy to drive a current through the tissue to be ablated, causing controlled, local heating, resulting in targeted tissue destruction.

**U.S. Food and Drug Administration (FDA):** The Acessa System (Halt Medical, Inc., Brentwood, CA) was given 510(k) approval in November 2012. According to the approval summary this system is indicated for use in percutaneous, laparoscopic coagulation and ablation of soft tissue, including treatment of symptomatic uterine fibroids under laparoscopic ultrasound guidance. The FDA specifically notes the Acessa System must be used under laparoscopic ultrasound guidance. Laparoscopic ultrasound equipment is not included with the Acessa System.

### **Literature Review**

Peer-reviewed published clinical trial data are limited to a single small randomized controlled trial of 51 women with 26 subjects in the RFA treatment arm (Brucker, 2014; Hahn, et al., 2015; Kramer, et al., 2016) and several nonrandomized, uncontrolled prospective studies, also with small participant numbers. Chudnoff et al. (2013), Guido et al. (2013) and Berman et al. (2014) reported 12-, 24- and 36-month follow-up of the same nonrandomized prospective interventional trial involving 135 women with symptomatic uterine fibroids. These studies are limited by uncontrolled, nonrandomized study design, small size and lack of comparison to other treatment methods. Several randomized controlled studies are ongoing.

Brucker et al. (2014) reported outcomes of a randomized, prospective single-center international clinical trial involving 51 women comparing radiofrequency volumetric thermal ablation (RFVTA) (n=26) and laparoscopic myomectomy (LM) (n=25) for symptomatic uterine fibroids. Primary outcomes were the mean hospital discharge times and perioperative outcomes. The predominant symptom reported by the patients in both groups was heavy menstrual bleeding followed by urinary frequency, pelvic discomfort and pain, backache, localized pain, dysmenorrhea, urinary retention, increased abdominal girth, dyspareunia, uterine pain, and sleep disturbance. There were no significant differences based on Fisher exact test between the two groups with regard to any of these symptoms, although the authors note this could be because of the relatively small number of patients in each group. Surgeons were blinded to the treatment until all fibroids were mapped by laparoscopic ultrasound. The mean hospitalization times were 10.0± 5.5 hours for the RFVTA group and 29.9 ± 14.2 hours for the LM group (p=.16). Intraoperative blood loss was 16 mL for the RFVTA procedures and 51 mL for the LM procedures. The percentage of fibroids imaged by laparoscopic ultrasound that were treated/excised was 98.6% for RFVTA and 80.3% for LM. Two complications were reported: vertigo (n=1; RFVTA) and port site hematoma (n=1; LM).



The mean time between arrival in post-anesthesia recovery and discharge from the hospital was 8.2 hours for the RFVTA group and 28.0 hours for the LM group ( $p < 0.001$ ). Mean hospitalization time was 10.0 hours and 29.9 hours for the RFVTA and LM groups, respectively,  $p < 0.001$ . The authors note that short-term follow-up is a limitation to the study and plan five-year follow-up for pregnancy outcomes, symptom improvement, and overall treatment satisfaction as evaluated on the basis of participants' responses to validated questionnaires. The study is limited by small study participant numbers.

Hahn et al. (2015) published one year results of the above study (Brucker, et al., 2014) with objective to analyze, compare and describe the study's three, six and twelve month outcomes in terms of pain medication use, recovery from surgery, and subjects' subjective responses to validated questionnaires. The results included: post-surgery, ablation and myomectomy subjects took pain medications for 4 days (range: 1–46) and 7 days (range: 1–83 days) respectively ( $p = 0.60$ ); ablation and myomectomy patients missed 10.0 workdays (range: 2–86 days) and 17.0 workdays (range: 7–30 days) ( $p = 0.28$ ); resumed normal activities in 20.5 days (range: 5–103 days) versus 28.0 days (range: 10–42 days) ( $p = 0.86$ ) respectively. The mean symptom severity scores decreased (improved) by  $-7.8$  for the ablation subjects and by  $-17.9$  for the myomectomy subjects ( $p = 0.16$ ). Health-related quality of life improved (increased) by 7.5 and 13.1, respectively, for the two groups ( $p = 0.46$ ). Two myomectomy subjects had pregnancies that ended in a Cesarean delivery and a vaginal delivery of healthy infants. Two pregnancies in the RFVTA group ended in full-term vaginal deliveries of healthy infants. The authors concluded that early postoperative recovery and twelve-month results indicate similar efficacy, quality of life, and safety for both treatment groups. The subjects will be continued to be followed for five years.

Kramer et al. (2016) reported on 24 month data from the above study (Brucker, et al., 2014). The outcomes included this analysis were patients' responses to validated questionnaires and long-term safety. The study included 51 patients with 21 and 22 patients in the RFVTA and laparoscopic myomectomy groups, respectively that completed 24 months of follow-up. There was improvement reported in the severity of symptoms from baseline by participants in both the RFVTA ( $P < 0.001$ ) and laparoscopic myomectomy groups ( $P = 0.001$ ). The study observed a significant improvement in health-related quality of life in the laparoscopic myomectomy group ( $P = 0.040$ ); and a non-significant improvement was noted in the RFVTA group ( $P = 0.083$ ). A trocar-site hematoma occurred in one patient in the laparoscopic myomectomy group. There were further surgical interventions recorded in three patients in the RFVTA group but it was noted that these were unrelated to fibroid symptoms.

Hayes evaluated the safety and efficacy the Acessa System for treatment of uterine fibroids (Hayes, 2014; 2017). They noted that the all of the included studies found significant benefits of treatment of uterine fibroids with the Acessa System, and longer-term studies demonstrated the durability of the treatment effect. Treatment reduced pain, heavy bleeding, and other symptoms, and improved quality of life. They found that the overall quality of the evidence is low. Five of the six studies lacked a control group, and the single, randomized, clinical trial only reported on perioperative outcomes with no long-term follow-up. Many of the study endpoints were subjective. Additional studies evaluating larger populations and that include control groups and head-to-head comparisons with other treatments for uterine fibroids are warranted to determine the optimal clinical role of this technology.

Chudnoff et al. (2013) reported one year results of a prospective, multicenter, interventional clinical trial (i.e., HALT trial) with primary outcome measures of change from baseline to 12 months and ongoing qualitative follow-up of women for three years in a cohort of 135 premenopausal symptomatic women with uterine myomas, uteri 14 weeks of gestation-sized or less with no single myoma exceeding 7 cm, and objectively confirmed heavy menstrual bleeding. Primary intervention was outpatient laparoscopic ultrasound-guided radiofrequency volumetric thermal ablation using the Acessa system (Halt Medical, Brentwood, CA). Bleeding outcomes and validated quality-of-life and patient satisfaction scales and objective measurements of uterine and myoma volume were conducted at 3, 6, and 12 months. Mean alkaline hematin and associated menstrual blood loss decreased from baseline levels by 31.8%, 40.7%, and 38.3%, respectively, at three-, six-, and 12-month intervals ( $p < .001$  for all). Symptom severity and health-related quality of life improved ( $p < .001$ ). There was one serious adverse event (0.7%) requiring readmission 5 weeks post-procedure and one surgical reintervention for persistent bleeding. Ninety-four percent of the women reported satisfaction with the treatment ( $p < .001$ ). The study was limited by uncontrolled design, short-term follow-up and a lack of comparison to other treatment methods.



In a follow-up to the study by Chudnoff et al. (2013), Guido et al. (2013) reported two-year outcomes of 124 subjects who participated in the HALT trial, of whom 112 were evaluable. Outcome measures included: subject responses to validated questionnaires, treatment-emergent adverse events, and surgical re-intervention for fibroids at 24 months post-procedure. Significant changes from baseline were noted in symptom severity ( $p < .001$ ) and health-related quality of life scores ( $p < .001$ ). There was a significant improvement in the mean health state score between baseline and 3 months after treatment ( $p < .001$ ). Measurements at subsequent intervals showed no continued improvement. Six patients underwent surgical reintervention for fibroid-related bleeding between 12 and 24 months. The authors also reported on one patient who had an episode of bleeding post Cesarean section requiring receipt of six units of blood, which the study authors noted as possibly related to the RFA procedure. Limitations to the study include uncontrolled design, lack of comparator, short-term follow-up and small total patient numbers.

In a thirty-six month follow-up study, Berman et al. (2014) reported subject responses to validated questionnaires and surgical repeat intervention to treat myomas outcomes for a cohort of 104 evaluable patients (104/135) who participated in the HALT trial. Change in mean symptom severity ( $p < .001$ ) and Health-Related Quality of Life questionnaire scores ( $p < .001$ ) were improved from the baseline. Patient-reported Uterine Fibroid Symptom and Health-Related Quality of Life questionnaire subscores demonstrated statistically significant improvement from baseline to 36 months ( $p < .001$ ) in all categories (i.e., Concern, Activities, Energy/Mood, Control, Self-consciousness, and Sexual Function). The cumulative repeat intervention rate was of 11% at 36 months. Although results are promising, study limitations include uncontrolled, nonrandomized design, lack of comparison to other treatment methods, and small study participant numbers.

Robles et al. (2013) assessed outcomes of a prospective study assessing the laparoscopic radiofrequency volumetric thermal ablation (RFVTA) system among 114 screened women with symptomatic myomas. Thirty-five women completed the 12-month follow-up period. Uterine fibroid symptom and health-related quality-of-life (UFS-QOL) questionnaires were completed at zero, three-, six-, and 12-months. There was a significant reduction in average symptom severity score over the study period ( $p < 0.001$ ), and reductions in symptom severity scores from baseline to each of the follow-up visits, and from the 3-month visit to the 12-month follow-up visit were significant ( $p < 0.001$ ). There was a significant increase in average health-related quality of life (HRQL) scores from baseline to 12 months ( $p < 0.001$ ) and in the HRQL scores from baseline to each of the follow-up visits ( $p < 0.001$ ). After discharge, none of the participants was admitted to hospital for procedure-related complications. Within the study period, none of the participants required hysterectomy or any myoma treatment after RFVTA. No transfusions were required. Nine adverse events among eight women were reported as definitely not device- or procedure-related. Study limitations which limit the ability to routine clinical practice include lack of randomization and control, small study population, short-term follow-up of 12 months and lack of comparison to other treatment methods.

Thirty-one women with symptomatic uterine fibroids underwent outpatient laparoscopic, ultrasound-guided, radiofrequency volumetric thermal ablation using the Halt 2000 System. Postoperative follow-up occurred at three, six, and 12 months. The primary outcome measures were patient safety, frequency of adverse events, repeat intervention rate, symptom severity and health-related quality-of-life scores from the validated Uterine Fibroid Symptom and Quality-of-Life Questionnaire. Secondary outcome measures were uterine volume changes over time. Mean symptom severity scores improved significantly compared with baseline at three, six, and 12 months. Mean health-related quality-of-life scores reached statistical significance over time. Mean uterine volume decreased at three six, and 12 months. There were no procedure-related repeat hospitalizations, repeat treatments or procedures related to fibroid symptoms following treatment. The study is limited by lack of randomization and control, short-term follow-up, small sample size and lack of comparison to other treatment methods. Larger multicenter studies are needed to confirm these results (Garza, 2011).

### **Professional Societies/Organizations**

#### **American Association of Gynecological Laparoscopists (AAGL):**

The AAGL published practice guidelines for the diagnosis and management of submucous leiomyomas (2012) which note with currently available evidence, embolic and ablative therapies, including leiomyoma ablation with radiofrequency electricity are not appropriate for women with submucous myomas who have current infertility or who wish to conceive in the future. The guidelines do not address embolic or ablative therapies related to submucous myomas for individuals without infertility or who do not desire future conception.



## Use Outside of the US

**Society of Obstetricians and Gynaecologists of Canada (SOGC):** the SOGC published evidenced-based guidelines for the management of uterine leiomyomas (Vilos, et al., 2015). The recommendations note that, “Of the conservative interventional treatments currently available, uterine artery embolization has the longest track record and has been shown to be effective in properly selected patients. (II-3) Newer focused energy delivery methods are promising but lack long-term data. (III)”. The newer methods included in this statement includes radiofrequency ablation of uterine fibroids.

Quality of evidence assessment:

III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

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### **Coding/Billing Information Obstetrics/Gynecology**

**Note:** 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

### **Obstetrics/Gynecology Services Considered Experimental/Investigational/Unproven:**

<b>CPT®* Codes</b>	<b>Description</b>
<a href="#">58674</a>	Laparoscopy, surgical, ablation of uterine fibroid(s) including intraoperative ultrasound guidance and monitoring, radiofrequency

**\*Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.**

### **Ophthalmology**

#### **Suprachoroidal Delivery of Pharmacological Agent (CPT Code 67299) Suprachoroidal Injection of a Pharmacologic Agent (does not include supply of medication (CPT code 0465T)**

The leading causes of blindness include those affecting the back of the eye: age-related macular degeneration, diabetic retinopathy, and uveitis. Although treatments are available, delivering drugs to the posterior regions of the eye is challenging because of architecture as well as natural barriers (Patel, 2011). Drug delivery techniques include intravitreal injections, periocular injections and intravitreal implants. Suprachoroidal drug delivery has been proposed as an alternative method to access the suprachoroid space (SCS). There have been several techniques described for injections into the SCS (Moisseiev, et al., 2016). The injection can be done using standard small-gauge needles, but this is a delicate procedure with a risk of penetration into the choroid or the vitreous cavity. Surgical cannulation may be used for drug delivery to the posterior pole, however, this is a complicated procedure and cannot be performed in-office. SCS drug delivery using microneedles is also being investigated. The micro-needles are small-gauge needles (30–33 G) and 0.7–1.0 mm in length that are only long enough to penetrate the sclera and reach the SCS. These microneedles have been demonstrated to be safe and effective in several animal studies. SCS™ microinjector (Clearside Biomedical Inc. Alpharetta, GA). is a microneedle being developed for SCS injection in humans. The device is currently undergoing two Phase 2 clinical trials with its proprietary formulation of triamcinolone acetonide (CLSTA) for the treatment of macular edema associated with noninfectious uveitis and along with aflibercept for the treatment of macular edema associated with RVO.

#### **U.S. Food and Drug Administration (FDA)**

The iScience Surgical Ophthalmic Microcannula (iScience Surgical Corporation, Redwood City, CA) is a flexible microcannula designed to allow atraumatic cannulation of spaces in the eye such as the anterior chamber and posterior segment (FDA, 2004). It received 510(k) approval on June 22, 2004 for the following indications: fluid infusion and aspiration, as well as illumination, during surgery.



SCS™ microinjector (Clearside Biomedical Inc. Alpharetta, GA) has not yet received FDA approval.

### **Literature Review**

Randomized control trial data are lacking to demonstrate the safety and effectiveness of suprachoroidal delivery of pharmacological agents for any indication, including injection of pharmacologic agents. Studies are limited by uncontrolled design and small populations.

### **Professional Societies/Organizations**

Guidelines of the American Academy of Ophthalmologists do not include suprachoroid delivery as a method for delivering drugs to the posterior regions of the eye.

### **Use Outside of the US**

No relevant information.

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### **Conjunctival Incision with Posterior Extrasceral Placement of a Pharmacological Agent (CPT Code 68399)**

Neovascular age-related macular degeneration (AMD) is associated with a rapid loss of vision due to an abnormal growth of blood vessels in the macula of the eye, leakage, and scarring (Geltzer, 2007). Treatment options for this disease are limited and there are a variety of therapies currently being investigated for neovascular AMD. Surgical implantation of steroids with antiangiogenic and anti-inflammatory properties has been proposed as a practical method of administering these agents into the eye (Geltzer, 2007). Extrasceral placement of steroids involves an incision into the orbit posterior to the limbus, through the conjunctiva. A cannula is inserted outside the sclera until the tip is near the macula, and the drug is administered. Advantages to this procedure may include a reduced risk for retinal detachment and endophthalmitis (Geltzer, 2007).

### **Literature Review**

Randomized controlled trial (RCT) data are scarce regarding the safety and effectiveness of conjunctival incision with posterior juxtascleral placement of pharmacological agents.

Geltzer et al. (2013) reported on a Cochrane review which analyzed outcomes of three RCTs involving the administration of triamcinolone acetonide versus placebo, anecortave acetate versus placebo, and anecortave acetate versus photodynamic therapy for the treatment of age-related macular degeneration. One trial found posterior juxtrascleral depot of anecortave acetate may be effective in preventing severe vision loss. Overall the assessment noted weak evidence as to the benefits and harms of steroids with antiangiogenic properties for treating neovascular AMD by posterior juxtrascleral placement of drugs.



## Use Outside of the US

No relevant information.

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## Automated Evacuation of Meibomian Glands (CPT Code 0207T)

The meibomian glands are located on the eyelids and are responsible for the production of sebum. Sebum prevents the tear film from evaporating too quickly from the eye's surface. Meibomian gland dysfunction leads to decreased secretion and abnormal composition of the tear film lipid layer, which in turn can lead to blockage of the glands, dry eye, and infection. Conventional treatment includes eyelid washing, use of preservative-free tears, omega-3 dietary supplementation, topical and oral antibiotics, corticosteroids, warm compresses and gentle eyelid massage. The use of an automated heated compression device has been proposed as a treatment of meibomian gland dysfunction.

## U.S. Food and Drug Administration

The LipiFlow Thermal Pulsation System (TearScience, Morrisville, NC) received FDA 510(k) clearance in July, 2011. This system is intended to be used by a physician in an in-office procedure. The FDA approval indicates "The LipiFlow Thermal Pulsation System is intended for the application of localized heat and pressure therapy in adult patients with chronic cystic conditions of the eyelids, including meiboman gland dysfunction (MGD) also known as evaporative dry eye or lipid deficiency dry eye."

## Literature Review

Blackie, et al (2017) conducted a prospective, multicenter, open-label clinical trial that included 200 subjects (400 eyes) who were randomized to a single VTP treatment (treatment group) or twice-daily, 3-month, conventional warm compress and eyelid hygiene therapy (control group). Control group subjects received crossover VTP treatment at 3 months (crossover group). Effectiveness measures of meibomian gland secretion (MGS) and dry eye symptoms were evaluated at baseline and one, three, six, nine and 12 months. Subjects with inadequate symptom relief could receive additional meibomian gland dysfunction therapy after 3 (treatment group) and 6 months (crossover group). At three months, the treatment group had greater mean improvement in MGS ( $P<0.0001$ ) and dry eye symptoms ( $P=0.0068$ ), compared to controls. At 12 months, 86% of the treatment group had received only one VTP treatment, and sustained a mean improvement in MGS from  $6.4\pm3.7$  (baseline) to  $17.3\pm9.1$  ( $P<0.0001$ ) and dry eye symptoms from  $44.1\pm20.4$  to  $21.6\pm21.3$  ( $P<0.0001$ ); 89% of the crossover group had received only one VTP treatment with sustained mean improvement in MGS from  $6.3\pm3.6$  to  $18.4\pm11.1$  ( $P<0.0001$ ) and dry eye symptoms from  $49.1\pm21.0$  to  $24.0\pm23.2$  ( $P<0.0001$ ). Greater mean improvement in MGS was associated with less severe baseline MGS ( $P=0.0017$ ) and shorter duration of time between diagnosis and treatment ( $P=0.0378$ ). The authors concluded that a single VTP treatment can deliver a sustained mean improvement in meibomian gland function and mean reduction in dry eye symptoms, over 12 months.



To compare the effectiveness of a single LipiFlow treatment with combined lid warming and massage in patients with meibomian gland dysfunction (MGD), Finis et al. (2014) published results of a prospective, randomized, crossover, observer-masked clinical trial involving 40 subjects. Subjects were randomized to receive either a single LipiFlow treatment (LipiFlow group) or to perform standardized, twice-daily combined lid warming and massage (lid margin hygiene or control group) for three months. The primary outcome measure was improvement of subjective symptoms, as assessed by the Ocular Surface Disease Index (OSDI) scores. Secondary outcome measures included improvement of TFBUT, decreased tear osmolality, increased LLT, and increased number of expressible meibomian glands. A total of 31 subjects completed the study. A total of 31 subjects completed the 3-month follow-up. At 1 and 3 months, patients in the LipiFlow treatment group had a significant reduction in Ocular Surface Disease Index (OSDI) scores compared with those in the lid-margin hygiene group ( $p < .01$ ). Both treatments produced a significant improvement in expressible meibomian glands compared to the baseline parameters, but no significant difference was noted between the two groups. The other investigated objective parameters did not show a significant difference. The authors note while results of this small study suggest that a single LipiFlow treatment is as least as effective as a 3-month, twice-daily lid margin hygiene regimen for MGD, the study was observer-masked only, and a placebo effect may have confounded any improvements in subjective symptoms and other parameters in both groups. Study limitations include non-blinded design and small study size. Larger, blinded randomized clinical trials are required to determine impact on health outcomes.

Lane et al. (2012) conducted a study examining the safety and effectiveness of the LipiFlow System compared with the iHeat Warm Compress (WC) for adults with meibomian gland dysfunction. This was a prospective open-label, randomized, crossover multicenter clinical trial. One hundred thirty-nine subjects were randomized between LipiFlow ( $n=69$ ) and WC control ( $n=70$ ). Subjects in the LipiFlow group received a 12-minute LipiFlow treatment and were reexamined at one day, two weeks and four weeks. Control subjects received a five-minute iHeat treatment with instructions to perform the same treatment daily for two weeks. At two weeks, they crossed over and received the LipiFlow treatment. LipiFlow resulted in significant improvement in meibomian gland secretion at two and four weeks ( $p < 0.05$ ). There was no change in meibomian gland secretion in the control group. Limitations to the study were the small population size. Results replicated in larger RCTs are required to demonstrate the ability to apply outcomes to the general population.

Mitra et al. (2005) reported results of a prospective, controlled, observer masked, single intervention trial in which 24 normal subjects were randomized into three groups: Group I: 10 minutes with the activated device, Group II: 10 minutes with the inactivated device, Group III: no intervention. The lipid layer thickness of each subject was measured prior and subsequent to the 10-minute period. A statistically significant increase in lipid layer thickness was seen in 87% of subjects in Group I ( $p < 0.001$ , left eye,  $p < 0.003$ , right eye.). Seventy-five percent of subjects experienced subjective improvement in ocular comfort. The authors note that meibomian therapy using this novel device results in increased lipid layer thickness. A limitation of this study was the small study population.

Korb et al. (2011) reported on a study attempting to determine the pressure required to express the first non-liquid material from nonfunctional lower lid meibomian glands, the pressure required to evacuate all of the expressible material from the glands, and the level of pain associated with these actions. Custom instrumentation was applied to the lower lid, exerting pressures from 1.0 to 150.0 pounds per square inch (psi). Pressure was monitored throughout the procedure as was pain level. The pressure required to obtain the first non-liquid material ranged between 5-40 pounds per square inch. Pain was the limiting factor for this treatment. Only 7% of the patients could tolerate the pressure necessary to administer complete expression of the non-liquid material.

### **Professional Societies/Organizations**

**American Academy of Ophthalmology (AAO) (2013):** the AAO preferred practice patterns for dry eye syndrome do not include automated heated compression device has been proposed as a treatment of meibomian gland dysfunction.

### **Use Outside of the US**

No relevant information.



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## **Insertion of Ocular Telescope Prosthesis Including Crystalline Lens (CPT Codes 0308T, HCPCS Code C1840)**

The prosthetic intraocular telescope system is intended for the treatment of central vision loss (bilateral central scotomas) due to age-related macular degeneration (AMD). The device projects an image onto the part of the retina which is still healthy and can still see images. The device not intended to cure AMD, however it has the potential to improve quality of life and daily functioning for patients with end-stage AMD. The implantation inside the eye allows the patient to use natural eye movements to see, rather than head movements, which are required when using external magnification devices for AMD-related low vision.

**U.S. Food and Drug Administration (FDA):** The Implantable Miniature Telescope™ (VisionCare Ophthalmic Technologies, Saratoga, CA) received FDA premarket approval in July 2010. According to the FDA, this device is an implantable device which, when combined with the optics of the cornea, constitutes a telephoto system for improvement of visual acuity in patients with severe to profound vision impairment due to bilateral, end-stage, age-related macular degeneration (AMD). The implantable miniature telescope (IMT) is surgically implanted in the capsular bag and is held in position by haptic loops. The intraocular telescope is available in two models: Wide Angle (WA) 2.2X and Wide Angle (WA) 2.7X. Both models are indicated for monocular implant. The implanted eye provides central vision, while the fellow eye continues to be used for peripheral vision.

The initial FDA approval noted the device is intended to improve vision in patients 75 years of age or older with stable, severe to profound vision impairment caused by end-stage age-related macular degeneration. The device is indicated for (FDA, 2010):

- monocular implantation to improve vision in patients greater than or equal to 75 years of age with stable, severe to profound vision impairment (best corrected distance visual acuity 20/160 to 20/800) caused by bilateral central scotomas associated with endstage age-related macular degeneration.
- Patients must:
  - have retinal findings of geographic atrophy or disciform scar with foveal involvement, as determined by fluorescein angiography;
  - have evidence of visually significant cataract (> grade 2)



- agree to undergo presurgery training and assessment (typically 2 to 4 sessions) with low vision specialists (optometrist or occupational therapist) in the use of an external telescope sufficient for patient assessment and for the patient to make an informed decision;
- achieve at least a 5-letter improvement on the ETDRS chart with an external telescope;
- have adequate peripheral vision in the eye not scheduled for surgery; and 6) agree to participate in postoperative visual training with a low vision specialist.

In October 2014, the FDA expanded the age limit for Implantable Miniature Telescope (IMT) to 65 years of age or older. The supplement also included revisions to the professional and patient labeling with updated data based on the results out to eight years post IMT implantation; to revise the acceptance of risk and informed decision agreement; and to the professional and patient labeling to emphasize that the longer the IMT is in the eye, the greater the potential risk of developing vision-impairing corneal edema which may lead to the need for corneal transplant and possible telescope removal.

As part of the initial approval, there was a requirement for extended follow-up of the premarket cohort population. According to the FDA, this continued follow-up of individuals in the long-term follow-up cohort (5 years postoperatively) will be conducted to provide additional long-term (up to eight years) safety data. The FDA also requires a multicenter, prospective, open label, single group assignment cohort study for safety. The study is required to consecutively will enroll 770 presurgical subjects aged 75 years and older with severe to profound vision impairment caused by end-stage age-related macular degeneration and a cataract. The subjects enrolled and undergoing implantation of the IMT will be followed for a total of five years with approximately six follow-up visits during the first year followed by annual visits thereafter for the next four years (FDA, 2010).

According to the FDA Summary Of Safety And Effectiveness implantation of the device is contraindicated in patients (FDA, 2010):

- Stargardt's macular dystrophy
- central anterior chamber depth (ACD) <3.0 mm; measurement of the ACD should be taken from the posterior surface of the cornea (endothelium) to the anterior surface of the crystalline lens.
- presence of corneal guttata.
- minimum age and endothelial cell density requirements are not met
- with cognitive impairment that would interfere with the ability to understand and complete the Acceptance of Risk and Informed Decision Agreement or prevent proper visual training/rehabilitation with the device
- who have evidence of active choroidal neovascularization (CNV) on fluorescein angiography or treatment for CNV within the past six months
- with any ophthalmic pathology that compromises the patient's peripheral vision in the fellow eye
- with previous intraocular or cornea surgery of any kind in the operative eye, including any type of surgery for either refractive or therapeutic purposes
- who have prior or expected ophthalmic related surgery within 30 days preceding intraocular telescope implantation
- with a history of steroid-responsive rise in intraocular pressure (IOP), uncontrolled glaucoma, or preoperative IOP >22 mm Hg, while on maximum medication
- with known sensitivity to post-operative medications
- who have a history of eye rubbing or an ocular condition that predisposes them to eye rubbing
- in whom the planned operative eye has:
  - myopia > 6.0 D
  - hyperopia > 4.0 D
  - axial length < 21 mm
  - a narrow angle, i.e., < Schaffer grade 2
  - cornea stromal or endothelial dystrophies, including guttata
  - inflammatory ocular disease
  - zonular weakness/instability of crystalline lens, or pseudoexfoliation
  - diabetic retinopathy



- untreated retinal tears
- retinal vascular disease
- optic nerve disease
- a history of retinal detachment
- intraocular tumor
- retinitis pigmentosa.
- in eyes in which both haptics cannot be placed within the capsular bag during surgery, the intraocular telescope should be removed and replaced with a conventional intraocular lens (IOL); sulcus fixation of either one or both haptics increases the risk of severe endothelial cell loss and corneal transplant

## Literature Review

Hudson et al. (2006) reported on a prospective, open-label, multicenter clinical trial (IMT-002 clinical trial) with fellow eye controls. The trial included 217 patients with AMD and moderate to profound bilateral central visual acuity loss (20/80-20/800) resulting from bilateral untreatable geographic atrophy, disciform scars. A visual prosthetic device (implantable telescope), designed to enlarge retinal images of the central visual field, was implanted monocularly in the capsular bag after lens extraction. Fellow eyes were not implanted to provide peripheral vision and served as controls. Study patients participated in six visual rehabilitation visits after surgery. At one year, 67% of implanted eyes achieved a 3-line or more improvement in best-corrected distance visual acuity (BCDVA) versus 13% of fellow eye controls ( $P < 0.0001$ ). Fifty-three percent of implanted eyes achieved a 3-line or more improvement in both BCDVA and BCNVA versus 10% of fellow eyes ( $P < 0.0001$ ). Mean BCDVA and best-corrected near visual acuity (BCNVA) improved 3.5 lines and 3.2 lines, respectively, in implanted eyes versus 0.8 lines and 1.8 lines, respectively, in fellow eyes ( $P < 0.0001$ ). Eleven eyes did not receive the device because of an aborted procedure. Endothelial cell density was reduced by 20% at three months and 25% at one year. The decrease in Endothelial cell density (ECD) was correlated with postsurgical edema ( $P < 0.0001$ ) with no evidence that endothelial cell loss is accelerated by ongoing endothelial trauma after implantation, the authors concluded that the device can improve visual acuity and quality of life in patients with moderate to profound visual impairment caused by bilateral, end-stage AMD.

Hudson et al. (2008) reported on two year results of the above study. The main outcome measures included BCVA change from baseline, endothelial cell density (ECD) and morphometry, and incidence of complications. At two years, data from 174 (92.6%) of 188 available patients were analyzed with findings that overall, 103 (59.5%) of 173 telescope-implanted eyes gained three lines or more (doubling of visual angle) of BCVA compared with 18 (10.3%) of 174 fellow control eyes ( $P < .0001$ ). Mean BCVA improved 3.6 lines (standard deviation [SD], 1.9 lines) and 2.8 lines (SD, 2.3 lines) from baseline in eyes with the 3X and 2.2X device models, respectively. Mean ECD stabilized through two years, with 2.4% mean cell loss occurring from one to two years. There was no significant change in coefficient of variation or percentage of hexagonal endothelial cells from within six months to two years after surgery. The most common complication found to be inflammatory deposits. The authors concluded that long-term results of this telescope prosthesis indicate the substantial BCVA improvement at one year is maintained at two years with the key indicators of corneal health demonstrating ECD change that reflects remodeling of the endothelium associated with the implantation procedure and no that there is no evidence of any ongoing endothelial trauma.

Boyer et al. (2015) reported on the long-term results (60 months) of implantable miniature telescope (IMT) in patients with bilateral, end-stage, age-related macular degeneration (AMD) (studies above Hudson, et al., 2006; Hudson et al., 2008). A subgroup analysis was performed with stratification for age (patient age 65 to <75 years [group 1; n=70] and patient age  $\geq 75$  years [group 2; n=127]), with a comparative evaluation of change in best-corrected distance visual acuity (BCDVA), quality of life, ocular complications from surgery, adverse events, and endothelial cell density (ECD). The mean BCDVA improvement from baseline to 60 months was  $2.41 \pm 2.69$  lines in all patients (n=76), with  $2.64 \pm 2.55$  lines in group 1 and  $2.09 \pm 2.88$  lines in group 2. The quality of life scores were significantly higher in group 1. The most common significant surgery-related ocular complications in group 1 were iritis >30 days after surgery (7/70; 10%) and persistent corneal edema (3/70; 4.3%); and in group 2 were a decrease in BCDVA in the implanted eye or IMT removal (10/127 each; 7.9%), corneal edema >30 days after surgery (9/127; 7.1%), and persistent corneal edema (6/127; 4.7%). The significant adverse events included four corneal transplants, comprising two (2.9%) in group 1 and two (1.6%) in group 2. At 60 months, one patient in group 1 (3.2%) and three patients in group 2 (9.4%) had lost  $\geq 2$  lines of vision. The IMT was removed in one (1.4%) and ten (7.9%) patients in group 1 and group 2, respectively. Mean ECD loss was 20% at 3 months.



Chronic loss was 3% per year. ECD loss was less in group 1 than in group 2 (35% versus 40%, respectively) at 60 months. These long-term results indicate substantial retention of improvement in BDCVA. The chronic ECD loss appears consistent with that reported for conventional intraocular lenses. The results indicate that younger patients retained more vision than their older counterparts with fewer adverse events.

### **Use Outside of the US**

National Institute for Health and Care Excellence (NICE) published guidelines for miniature lens system implantation for advanced age-related macular degeneration. The guidelines note (NICE, 2016) that, "Evidence on the efficacy of miniature lens system implantation for advanced age-related macular degeneration (AMD) shows that the procedure can improve both vision and quality of life in the short term. Data on short-term safety are available for limited numbers of patients. There is currently insufficient long-term evidence on both efficacy and safety. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research."

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### **Quantitative Pupillometry (CPT Code 0341T)**

Pupil reactivity and sensitivity may indicate neurological issues or worsening of neurological status. Current practice is to use a penlight to observe the pupillary light reflex which is a subjective measurement. Several quantitative pupillometer devices are available, although their use is primarily restricted to the research setting (Couret, et al., 2016). The stimulation and subsequent measurement of pupil reactivity by a hand held infrared camera and use of a digital device and data processor to calculate measurements has been proposed for a number of indications including the evaluation of autonomic function, response to pain, drug metabolism, sleep disorders, and various psychological indications and has been use in the research setting. A pupillometer is made of three components: the light source to stimulate the pupil, an image capturing device capable of taking measurements of the pupil in real-time, and a data processor that performs the calculations using the measurements. The device is held in the patient's visual field, the data is interpreted, and a report is generated.

### **Literature Review**

High level, randomized and controlled data are lacking regarding the effectiveness of this device in the published, peer viewed scientific literature.



Couret et al. (2016) reported on study that compared automated quantitative pupillometry with the standard clinical pupillary examination currently used for brain-injured patients. Repetitive measurements were made in 200 healthy volunteers providing a total of 400 paired (alternative right eye, left eye) measurements under a wide variety of ambient light condition with the NeuroLight Algiscan pupillometer and then a prospective, observational, double-blinded study was conducted in two neurocritical care units. In 200 healthy volunteers, intra-class correlation coefficient for maximum resting pupil size was 0.95 (IC: 0.93-0.97) and for minimum pupil size after light stimulation 0.87 (0.83–0.89). It was found 3-pupil asymmetry ( $\geq 1$  mm) in these volunteers (1.5 % of the population) with a clear pupil asymmetry during clinical inspection. The mean pupil light reactivity was  $40 \pm 7$  %. In 59 patients, 406 pupillary measurements were prospectively performed. Concordance between measurements for pupil size collected using the pupillometer, versus subjective assessment, was poor (Spearman's rho = 0.75, IC: 0.70-0.79;  $P < 0.001$ ). A global rate of discordance of 18 % (72/406) was found between the two techniques when assessing the pupillary light reflex. For measurements with small pupils (diameters  $< 2$  mm) the error rate was 39 % (24/61). The results demonstrated that pupillary evaluations obtained subjectively at the patient's bedside were inaccurate compared with those obtained with an automatic quantitative pupillometer device. The authors concluded that the standard practice in pupillary monitoring yields inaccurate data, that automated quantitative pupillometry is a appears to be a more reliable method with which to collect pupillary measurements at the bedside; however, the impact of a pupillometer use on patients' outcome has to be demonstrated in further prospective studies.

In a cross-sectional cohort study Kantor et al. (2014) assessed the association between postoperative pain (NRS) and pupillary diameter or pupillary light reflex amplitude (PLRA) in 145 Post Anesthesia Care Unit (PACU) patients after routine anesthetic care. Sedation, hemodynamic, pupillary and pain assessments were performed in each patient after their arrival in the PACU or before morphine titration. In patients receiving morphine titration, a second assessment was performed after titration. Sedation was assessed using the modified Observer's Assessment of Alertness/Sedation (OAAS) scale. Hemodynamic assessment consisted of non-invasive systolic and diastolic blood pressure and heart rate. Pupillary assessment was performed with an infrared portable dynamic videopupillometer. Mean numerical rating score (NRS) for pain as assessed by study participants was 4.7, and was more than four in 79 patients (55%). No statistically significant association was observed between NRS and pupillary diameter ( $p=0.54$ ). Twenty-seven patients (19%) received morphine titration with significant decreases in NRS, pupillary diameter and PLRA afterwards. No association was observed between NRS changes and pupillary diameter or PLRA changes. The authors concluded acute postoperative pain is not associated with pupillary diameter or PLRA. Further high quality randomized clinical trial data is required to demonstrate the impact of pupillometry as a means to assess pain in the PACU.

Bremner et al. (2006) reported results of a prospective study of involving the use of light reflex pupillography in 150 consecutive patients with symptomatic generalized autonomic failure. Inclusion criteria was heterogeneous with a variety of indications represented including amyloidosis, multiple system atrophy, pure autonomic failure, diabetes mellitus, hereditary neuropathies, and paraneoplastic syndromes. Infra-red video pupillography was used to measure resting pupil diameters in light and dark, the light reflex response, the miosis associated with an accommodative effort, and responses to topical administration of various pharmacological agents. No significant correlation between the type of pupil abnormality and the predominant type of systemic autonomic deficit was seen in most conditions. The authors note "Although there does appear to be some weak correspondence between our pupillographic findings and the results of autonomic function tests, a  $\chi^2$  test suggests that this association could have arisen by chance ( $p=0.072$ )."

### **Professional Societies/Organizations**

**American Academy of Ophthalmology (AAO) (2013):** The Guidelines for recommendations for keratorefractive laser surgery notes that measurement of pupil size is not required in the preoperative examination.

### **Use Outside of the US**

No relevant information

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#### **Visual Field Assessment with Concurrent Real Time Data Analysis (CPT Codes 0378T, 0379T)**

Visual field assessment is reported for up to 30 days. The patient transmits daily test-data to monitoring center (IDTF) for input into secured database. The technician with physician analyzes the data and prepares report and the results are then interpreted by a physician.

#### **Literature Review**

There is insufficient evidence in the published, peer-reviewed scientific literature to establish improved health outcomes with this testing. At this time the role of this service has not been established.

#### **Professional Societies/Organizations**

Professional society guidelines are lacking regarding visual field assessment with concurrent real time data analysis.

#### **Use Outside of the US**

No relevant information

#### **References**

#### **Computer-Aided Animation and Analysis of Time Series Retinal Images for the Monitoring of Disease Progression (CPT Code 0380T)**

MatchedFlicker® (EyeIC Inc., Wayne, PA) is a device that is purported to enable fast and accurate comparison of digital fundus images to aid clinicians in diagnosis. According to the vendor's website, MatchedFlicker automatically combines time-series images selected from a patient record to create an animation wherein images are aligned, superimposed and alternated back and forth.

There is insufficient evidence in the published, peer-reviewed scientific literature to establish improved health outcomes using this technology. At this time the role of computer-aided animation and analysis of time series retinal images to monitor disease progression has not been established.

#### **Literature Review**

There is insufficient evidence in the published, peer-reviewed scientific literature to establish improved health outcomes with this testing. At this time the role of this service has not been established.

#### **Professional Societies/Organizations**

Professional society guidelines are lacking regarding computer-aided animation and analysis of time series retinal images for the monitoring of disease progression.

#### **Use Outside of the US**

No relevant information



## References

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### **Retinal prosthesis system (Device evaluation, interrogation, and initial programming of intra-ocular retinal electrode array) (CPT codes 0100T, 0472T, 0473T, C1841, C1842)**

Retinitis pigmentosa (RP) comprises a complex group of inherited dystrophies characterized by progressive degeneration and dysfunction of the retina, primarily affecting photoreceptor and pigment epithelial function. The clinical manifestations of RP include night blindness, loss of peripheral vision from progressive loss of photoreceptors, and variably loss of central vision due to cataracts and macular edema (Garg [UpToDate], 2017). The Argus II Retinal Prosthesis System (Argus II) (Second Sight Medical Products, Inc. Sylmar, CA) is intended to provide electrical stimulation of the retina to elicit visual perception in blind individuals with severe to profound retinitis pigmentosa. The implant is an epiretinal prosthesis that is surgically implanted in and on the eye that includes an antenna, an electronics case, and an electrode array. The external equipment includes glasses, a video processing unit (VPU) and a cable.

**U.S. Food and Drug Administration (FDA):** The Argus II Retinal Prosthesis System received a Humanitarian Device Exemption (HDE) from the FDA in February 2013. This device is indicated for use in patients with severe to profound retinitis pigmentosa who meet the following criteria:

- Adults, age 25 years or older.
- Bare light or no light perception in both eyes. (If the patient has no residual light perception, then evidence of intact inner layer retina function must be confirmed.)
- Previous history of useful form vision.
- Aphakic or pseudophakic. (If the patient is phakic prior to implant, the natural lens will be removed during the implant procedure.)
- Patients who are willing and able to receive the recommended post-implant clinical follow-up, device fitting, and visual rehabilitation.

## Literature Review

Agency for Healthcare Research and Quality (AHRQ) published a technology assessment for retinal prostheses systems (RPS) in the Medicare population (Fontanarosa, et al., 2016). The review included 30 publications of 11 RPS studies. The report notes that, "Although some patients clearly experienced improved visual acuity, visual field, and visual function, the percentages varied greatly among studies of Moderate to High risk of bias. Thus, evidence is insufficient to estimate the proportion of patients who will benefit from an RPS." The report concluded that some patients clearly benefit from implantation with an RPS, but determining who those patients are is still a challenge. Future studies of retinal prostheses devices should make an effort to report valid and reliable measures of important outcomes, especially day-to-day function and quality of life (QoL).

Dagnelie et al. (2017) conducted a study with the objective to test 28 Argus II subjects, all profoundly blind on three real-world functional vision tasks. Subjects were tested on the three real-world functional vision tasks: Sock Sorting, Sidewalk Tracking and Walking Direction Discrimination task. The mean percentage correct OFF versus ON for the Sock Sorting task was found to be significantly different for both testing conditions (t-test,  $P < 0.01$ ). On the Sidewalk Tracking task, subjects performed significantly better with the system ON than they did with the system OFF (t-test,  $P < 0.05$ ). Eighteen (18) of 27 subjects (67%) performed above chance with the system ON, and 6 (22%) did so with system OFF on the Walking Direction Discrimination task. The authors concluded that Argus II subjects performed better on all three tasks with their systems ON than they did with their systems OFF. The study is limited by the small number of subjects and needs to be confirmed in a larger study.

Da Cruz conducted a prospective, multicenter, single-arm, clinical trial of 30 subjects in 10 centers in US and Europe to study the long-term safety and efficacy of the Argus II System in patients with bare or no light perception due to end-stage RP. Within-patient controls included the non-implanted fellow eye and patients' native residual vision compared to their vision when using the System. The primary outcome measures were safety (the number, seriousness, and relatedness of adverse events) and visual function, as measured by three computer-based, objective tests. Secondary measures included functional vision performance on objectively-



scored real-world tasks. Twenty-four out of 30 patients remained implanted with functioning Argus II Systems at 5 years post-implant. Only one additional serious adverse event was experienced since the three-year time point. Patients performed better with the System ON than OFF on all visual function tests and functional vision tasks. The authors concluded that the five-year results of the Argus II trial support the long-term safety profile and benefit of the Argus II System for patients blind from RP.

### **Professional Societies/Organizations**

Professional society guidelines are lacking regarding intra-ocular retinal electrode array for treatment of retinitis pigmentosa.

### **Use Outside of the US**

**Health Quality Ontario:** this organization published a health technology assessment for retinal prosthesis system for advanced retinitis pigmentosa (2017). The recommendation of the assessment notes, "The Ontario Health Technology Advisory Committee recommends publicly funding the Argus II retinal prosthesis system for advanced retinitis pigmentosa." The committee determined that the Argus II system has demonstrated clinical effectiveness in restoring partial functional vision for patients with advanced retinitis pigmentosa. The Ontario Health Technology Advisory Committee took into account value for money, as well as the lived experience of people with retinitis pigmentosa and noted that the Argus II system offers the possibility of quality-of-life improvements in a population for whom there is no other treatment option.

**National Institute for Health and Care Excellence (NICE):** NICE published interventional procedure guidance for insertion of epiretinal prosthesis and insertion of a subretinal prosthesis system for retinitis pigmentosa (NICE, 2015). The guidance includes these recommendations:

Subretinal prosthesis system:

- Current evidence on the safety and efficacy of insertion of a subretinal prosthesis system for retinitis pigmentosa is limited in quality and quantity. Therefore, this procedure should only be used in the context of research.
- NICE encourages further research on this procedure. Outcomes should include the impact on quality of life and activities of day-to-day living, and durability of implants.

Epiretinal prosthesis:

- Current evidence on the safety and efficacy of insertion of epiretinal prosthesis for retinitis pigmentosa is limited in quality and quantity. Therefore, this procedure should only be used in the context of research.
- NICE encourages further research on this technology. Outcomes should include the impact on quality of life and activities of day-to-day living, and durability of implants.

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### **Coding/Billing Information Ophthalmology**

**Note:** 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

### **Insertion of Ocular Telescope Prosthesis Including Crystalline Lens**

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

<b>CPT® Codes</b>	<b>Description</b>
<a href="#">0308T</a>	Insertion of ocular telescope prosthesis including removal of crystalline lens or intraocular lens prosthesis

<b>HCPCS Codes</b>	<b>Description</b>
<a href="#">C1840</a>	Lens, intraocular (telescopic)

### **Ophthalmology Services Considered Experimental/Investigational/Unproven:**

<b>CPT® Codes</b>	<b>Description</b>	<b>Comment</b>
<a href="#">67299</a>	Unlisted procedure, posterior segment	Considered Experimental/Investigational/Unproven when used to report suprachoroidal delivery of pharmacologic agent
<a href="#">68399</a>	Unlisted procedure, conjunctiva	Considered Experimental/Investigational/Unproven when used to report conjunctival incision with posterior extrac scleral placement of a pharmacologic agent
<a href="#">0100T</a>	Placement of a subconjunctival retinal prosthesis receiver and pulse generator, and implantation of intra-ocular retinal electrode array, with vitrectomy	
<a href="#">0207T</a>	Evacuation of meibomian glands, automated, using heat and	



	intermittent pressure, unilateral	
<a href="#">0341T</a>	Quantitative pupillometry with interpretation and report, unilateral or bilateral	
<a href="#">0378T</a>	Visual field assessment, with concurrent real time data analysis and accessible data storage with patient initiated data transmitted to a remote surveillance center for up to 30 days; review and interpretation with report by a physician or other qualified health care professional	
<a href="#">0379T</a>	Visual field assessment, with concurrent real time data analysis and accessible data storage with patient initiated data transmitted to a remote surveillance center for up to 30 days; technical support and patient instructions, surveillance, analysis, and transmission of daily and emergent data reports as prescribed by a physician or other qualified health care professional	
<a href="#">0380T</a>	Computer-aided animation and analysis of time series retinal images for the monitoring of disease progression, unilateral or bilateral, with interpretation and report	
<a href="#">0465T</a>	Suprachoroidal injection of a pharmacologic agent (does not include supply of medication)	
<a href="#">0472T</a>	Device evaluation, interrogation, and initial programming of intraocular retinal electrode array (eg, retinal prosthesis), in person, with iterative adjustment of the implantable device to test functionality, select optimal permanent programmed values with analysis, including visual training, with review and report by a qualified health care professional	
<a href="#">0473T</a>	Device evaluation and interrogation of intraocular retinal electrode array (eg, retinal prosthesis), in person, including reprogramming and visual training, when performed, with review and report by a qualified health care professional	

HCPCS Codes	Description
<a href="#">C1841</a>	Retinal prosthesis, includes all internal and external components
<a href="#">C1842</a>	Retinal prosthesis, includes all internal and external components; add-on to C1841

**\*Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.**

## **Oncology**

### **Tumor Treatment Fields Therapy (e.g., Optune™) (HCPCS Codes A4555, E0766)**

Electric tumor treatment fields (TTF) therapy, also known as alternating electric field therapy, has been proposed for the treatment of recurrent glioblastoma multiforme (GBM). Inferred mechanism of action is disruption of the rapid cell division exhibited by cancer cells by alternating electrical currents applied to the brain through electrically insulated surface transducer arrays which are placed on the patient's shaved scalp. The fields alter the tumor cell polarity at an intermediate frequency. The frequency used for a particular treatment is specific to the cell type being treated (NovoCure, 2014).

At this time, Optune™ (formerly the NovoTTF-100A System) (Novocure, Portsmouth, NH) is the only TTF device that has received FDA approval electric tumor fields therapy. This system is a wearable, non-invasive, portable battery or power-supply operated device designed for continuous use throughout the day or night. It produces continuous TTF treatment at 100-200kHz. TTF are applied to two pairs of insulated electrode arrays in an alternating fashion. The electrodes are placed on the scalp over a layer of adhesive hydrogel which is held in place by adhesive strips. The scalp must be re-shaved to maintain optimal contact between the electrode and



the skin. Gel under the electrodes requires replacement every three-four days. The treatment period is for a minimum of four weeks.

### **U.S. Food and Drug Administration (FDA)**

The NovoTTF-100A System (Portsmouth, NH) was granted premarket approval (PMA) by the FDA in April, 2011. This device is indicated for treatment of adult patients who are 22 years of age or older who have histologically-confirmed glioblastoma multiforme (GBM), following histologically-or radiologically confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted. The pre-market approval requires a post market nonrandomized, unblinded, concurrent control study to be undertaken using the NovoTTF-100A system in patients with recurrent GBM (FDA, 2011).

In October 2015, the FDA approved an expanded indication for the Optune device to treat patients with newly-diagnosed glioblastoma multiforme (GBM), an aggressive form of brain cancer. It is given along with the chemotherapy drug temozolomide (TMZ) following standard treatments that include surgery, and radiation therapy and chemotherapy used together.

### **Literature Review**

Stupp et al. (2015) reported on an interim analysis of a multicenter, open-label, randomized phase 3 trial designed to test the efficacy and safety of TTFields in combination with temozolomide for treatment of glioblastoma after initial treatment with chemoradiation. The study included 210 patients randomized to TTFields plus temozolomide and 105 patients randomized to temozolomide alone, and conducted at a median follow-up of 38 months. Results included that median progression-free survival in the intent-to-treat population was 7.1 months (95%CI, 5.9-8.2 months) in the TTFields plus temozolomide group and 4.0 months (95%CI, 3.3-5.2 months) in the temozolomide alone group (hazard ratio [HR], 0.62 [98.7%CI, 0.43-0.89];  $P=.001$ ). Median overall survival in the per-protocol population was 20.5 months (95%CI, 16.7-25.0 months) in the TTFields plus temozolomide group ( $n=196$ ) and 15.6 months (95%CI, 13.3-19.1 months) in the temozolomide alone group ( $n=84$ ) (HR, 0.64 [99.4%CI, 0.42-0.98];  $P=.004$ ). The authors concluded that in this analysis of patient with glioblastoma who had completed standard chemoradiation therapy, the addition of TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival.

Stupp et al. (2017) reported on the final analysis randomized, trial noted above (Stupp, et al., 2015) of all 695 patients with median follow-up of 40 months and minimum follow-up of 24 months. Patients were randomized 2:1 to TTFields plus maintenance temozolomide chemotherapy ( $n = 466$ ) or temozolomide alone ( $n = 229$ ). The TTFields, consisting of low-intensity, 200 kHz frequency, alternating electric fields, was delivered ( $\geq 18$  hours/d) via 4 transducer arrays on the shaved scalp and connected to a portable device. Temozolomide was administered to both groups for 5 days per 28-day cycle (6-12 cycles). Progression-free survival (tested at  $\alpha = .046$ ). The secondary end point was overall survival (tested hierarchically at  $\alpha = .048$ ). Analyses were performed for the intent-to-treat population. Of the 695 patients 637 (92%) completed the trial. Median progression-free survival from randomization was 6.7 months in the TTFields-temozolomide group and 4.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.52-0.76;  $P < .001$ ). Median overall survival was 20.9 months in the TTFields-temozolomide group vs 16.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76;  $P < .001$ ). Systemic adverse event frequency was 48% in the TTFields-temozolomide group and 44% in the temozolomide-alone group. Mild to moderate skin toxicity underneath the transducer arrays occurred in 52% of patients who received TTFields-temozolomide compared to none in patients who received temozolomide alone.

Hayes published a directory report regarding Tumor Treating Fields (TTF) (Hayes, March 2016; 2018). The review concluded that although clinical trials have shown that Novocure is at least comparable with chemotherapy, the body of literature is small and individual studies are subject to serious limitations, including lack of a control or comparator group, high loss to follow-up, and lack of statistical comparisons. Additional evidence including randomized, controlled trials and cohort studies of sufficient size and design are needed to further investigate the safety and efficacy of Novocure in patients with recurrent and newly diagnosed glioblastoma and other cancers.



Data regarding the safety and effectiveness for TTF are limited in the published, peer-reviewed scientific literature and consist of several prospective studies and a randomized clinical trial (RCT) involving a total of 273 patients (Stupp, 2012; Kirson, 2009; Salzbeg, 2008; Kirson, 2007). In the prospective phase III RCT, Stupp et al. (2012) reported results of 237 individuals with recurrent GBM. Participants were randomized to TTF (n=120) versus physician's choice of chemotherapy (n=117). The study failed to reach its primary end-point of improved survival compared to active chemotherapy. Neither overall survival nor progression-free survival were significantly improved at six months in the group randomized to TTF versus chemotherapy (p=0.23 and 0.13, respectively). The authors noted that responses were more frequent in the group treated with TTF but this was not significant (p=0.19). Quality of life measurement favored TTF over chemotherapy for emotional and cognitive functioning; no significant difference was noted for global health and social functioning. Physical functioning favored the chemotherapy arm. TTF-related adverse events were mild (14%) to moderate (2%), usually involving skin rash beneath the transducer arrays. Severe adverse events occurred in 6% and 16% (p = 0.022) of patients treated with TTF and chemotherapy, respectively. Results do not demonstrate improved OS or PFS with TTF compared to active chemotherapy.

#### **NovoTAL™ (CPT code 64999)**

NovoTAL (Novocure, Portsmouth, NH) is software that may be used for treatment planning before the Optune treatment. According to vendor's website, NovoTAL is optional software that a physician can purchase and create individualized treatment maps for patients starting Optune. It is performed in-office. The physicians are required to complete training and certification in order to use the NovoTAL System. The Optune device is available preset from Novocure. The device is preset to deliver TTFields at a frequency of 200 kHz and is operated by the patient independently. It is monitored periodically by device specialists, who are available 24/7 to provide technical support to the patient, their family and physician (Trusheim, et al., 2017). The published literature does not indicate that the use of the software for treatment planning with Novotal is superior to using Optune with preset settings or that it improves clinical outcomes.

#### **Literature Review—NovoTAL**

Wenger et al. (2016) reported on a study with a human head model generated from MRI images of a healthy subject to investigate tumors of different size, shape, and location and the effect of varying transducer layouts on Tumor Treating Fields (TTF) distribution in an anisotropic model. Four different virtual tumors were placed at separate locations. The transducer arrays were modeled to mimic the TTF-delivering commercial device. For each tumor location, varying array layouts were tested. The finite element method was used to calculate the electric field distribution, taking into account tissue heterogeneity and anisotropy. In all tumors, the average electric field induced by either of the two perpendicular array layouts exceeded the 1-V/cm therapeutic threshold value for TTF effectiveness. Field strength within a tumor did not correlate with its size and shape but was higher in more superficial tumors. Additionally, it always increased when the array was adapted to the tumor's location. Compared with a default layout, the largest increase in field strength was 184%, and the highest average field strength induced in a tumor was 2.21 V/cm. The authors concluded that the result adapting transducer array layouts to specific tumor locations was highly beneficial, because it led to substantial increases in the induced field strength within the tumor and better TTF coverage in the affected areas.

Connelly et al. (2016) reported on a case series of eight patients where treating physician has utilized non-contrast enhancement and advanced imaging to inform tumor treatment fields (TTF) treatment planning based on a clinical evaluation of where a patient is believed to have active tumor. All patients presented with gliomas (grades 2–4). Each patient had previously received standard therapy including surgery, radiation therapy and/or chemotherapy prior to initiation of TTF and the majority had progressed on prior therapy. A standard pre- and postcontrast MRI scan was acquired and used for TTF treatment planning. The authors concluded that the case series details important approaches for integrating clinical considerations, nonmeasurable disease and advanced imaging into the treatment planning workflow for TTF. The author noted that as TTF become integrated into standard care pathways for glioblastoma, the case series demonstrates that treatment planning beyond the extent of contrast enhancement is clinically feasible and should be prospectively compared to standard treatment planning in a clinical trial setting, in order to determine the impact on patient outcomes.

Chaudry et al. (2015) reported on a study that evaluated performance of 14 physicians in conducting transducer array layout mapping using the NovoTAL System compared with mapping performed by the Novocure in-house clinical team. The physicians evaluated five blinded cases of recurrent glioblastoma and performed head size



and tumor location measurements using a standard Digital Imaging and Communications in Medicine reader. Concordance with Novocure measurement and intra- and inter-rater reliability were assessed using relevant correlation coefficients. The study criterion for success was a concordance correlation coefficient (CCC) >0.80. CCC for each physician versus Novocure on 20 MRI measurements was 0.96 (standard deviation, SD  $\pm$  0.03, range 0.90–1.00). Intra- and inter-rater reliability correlation coefficients were similarly high: 0.83 (SD  $\pm$  0.15, range 0.54–1.00) and 0.80 (SD  $\pm$  0.18, range 0.48–1.00), respectively. This user study has a low number of participants and while it appears that there is a high agreement between the two groups, it does not indicate that NovoTAL provides improved health outcomes compared to mapping provided by Novocure.

### Professional Societies/Organizations

**National Comprehensive Cancer Network<sup>™</sup> (NCCN<sup>™</sup>):** NCCN guideline for cancer of the central nervous system includes in the recommendation for treatment of recurrent disease, the option to consider alternating electric field therapy for recurrent disease for anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic astrocytoma, and glioblastoma. Category 2B\*

The 2018 update of the NCCN guidelines includes in the recommendation for treatment of glioblastoma (with supratentorial disease), adjuvant treatment, the option of using adjuvant temozolomide and alternating electric field therapy. Category 1\*

\*NCCN Categories of Evidence and Consensus:

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate (NCCNa, 2018).

### Use Outside of the US

A second generation Optune device has received placement of the CE Mark for use in the European Union.

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### **Coding/Billing Information Oncology**

**Note:** 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

### **Tumor Treatment Fields (TTF) Therapy (i.e., Optune™)**

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

<b>HCPSC Codes</b>	<b>Description</b>
<a href="#">A4555</a>	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
<a href="#">E0766</a>	Electrical stimulation device used for cancer treatment, includes all accessories, any type

**Considered Experimental/Investigational/Unproven when used to report treatment planning software (i.e., NovoTAL) for use with tumor treatment fields:**

<b>CPT® Codes</b>	<b>Description</b>	<b>Comment</b>
<a href="#">64999</a>	Unlisted procedure, nervous system	Considered Experimental/Investigational/



		Unproven when used to report treatment planning software (i.e., NovoTAL) for use with tumor treatment fields
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**\*Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.**

## **Otolaryngology**

### **Automated Audiometry Devices (CPT Codes 0208T, 0209T, 0210T, 0211T, 0212T)**

Audiometers measure and characterize hearing loss by determining an individual's hearing threshold. Conventional tests utilized for assessment include the behavioral pure-tone audiogram (hearing sensitivity of single-frequency signals) and speech recognition (hearing sensitivity for spoken material). These tests require interaction between the trained technician or audiologist and the patient. Conventional audiometry tests are performed manually and interpretation of the raw data is performed by the audiologist.

The use of automated audiometry devices has been proposed as an alternative to manually operated devices. Automated units use conventional technology; however, the equipment is fully automated. Results are displayed as pass or fail/refer and do not require further interpretation by a technician or audiologist. A failure score may result in further referral to a health care professional.

### **U.S. Food and Drug Administration (FDA)**

Several automated audiometric devices have received FDA 510 (k) approval. These include, but are not limited to: the AuDX Otoacoustic Emissions Measurement System with AuDX I/O Function (Natus Medical Incorporated, Mundelein, IL) received FDA 510(k) approval as an equivalent device in December 2011. The device is indicated for use when it is necessary for a trained health care professional to measure or determine cochlear function. The device can be used for patients of all ages, from newborn infants through adults to include geriatric patients. The otoacoustic emissions test is especially indicated for use in testing individuals for whom behavioral results are deemed unreliable, such as infants, young children, and cognitively impaired adults. The Otogram™ Hearing Diagnostic System (Ototronix Diagnostics, Houston, TX, formerly marketed by Tympany, Inc., Salt Lake City, UT) received FDA 510(k) approval as an equivalent device in March 2007. The device is indicated for use by trained healthcare professionals on both adults and pediatric subjects for measurement of audiometric parameters to identify and supply to help diagnose hearing loss and ear disorders.

### **Literature Review**

Although there are a number of cohort and case series reported in the published peer-reviewed scientific literature, randomized controlled trial, meta-analysis and systematic review data are lacking. In a nonrandomized comparison study by Lancaster et al. (2008) involving screening results of 32 children using on-site and telehealth screening methods the authors report identical otoscopic and immittance results. Pure-tone results were different between on-site and telehealth screening methods for five of 32 students. Using the on-site pure-tone screening protocol as the 'gold standard' the authors report that the tele-health pure-tone screening protocol yielded four false positive responses and one false negative response. This study was limited by uncontrolled study design and small study numbers.

### **Professional Societies/Organizations**

**American Academy of Pediatrics (AAP):** The AAP (Harlor, et al., 2009) published recommendations for hearing assessment in infants and children. These recommendations include discussion of automated auditory brainstem response (ABR) test as an objective physiologic means of hearing screening. The guideline does not mention the automation of other tests.

### **Use Outside of the US**

No relevant information.

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### **Transtympanic Micropressure Device for Ménière's Disease (e.g., Meniett™ Device) (HCPCS Code E2120)**

Ménière's disease (also called idiopathic endolymphatic hydrops) is a disorder of the inner ear. Although the cause is unknown, the disorder probably results from an abnormally large amount of fluid (called endolymph) collecting in the inner ear. The symptoms of Ménière's disease include episodic vertigo (i.e., a sensation of dizziness or spinning), hearing loss, tinnitus (i.e., ringing in the ears), and a sensation of fullness in the affected ear.

The use of a transtympanic micropressure device/low-pressure pulse generator (i.e., Meniett™) (Medtronic Xomed, Jacksonville, FL) has been proposed as an alternative to surgery. The device is prescribed by a physician and delivers low-frequency, low-amplitude pressure pulses within the range of 0–20 centimeter (cm) H<sub>2</sub>O to the middle ear via a close-fitting ear cuff and tympanostomy tube. Its mode of action is thought to be transmission of the pulses to the inner ear, promoting the flow of endolymph out of the cochlea, alleviating the hydrops and relieving symptoms. The tympanostomy tube is inserted under local anesthetic in the office setting. The patient then uses the device at home three times per day for approximately three minutes per session. The patient discontinues use when symptoms remit.

### **U.S. Food and Drug Administration (FDA)**

In December 1999, Pascal Medical AB (Sweden) received 510(k) approval from the FDA for the Meniett Low-Pressure Pulse Generator. In 2001, Medtronic Xomed, Inc. (Jacksonville, FL) purchased the device from Pascal Medical. The Meniett Low-Pressure Pulse Generator is classified as a Class II device and is indicated for the symptomatic treatment of Ménière's disease.

### **Literature Review**

Russo et al. (2017) conducted a randomized, double-blind, placebo-controlled, multicenter trial to evaluate the efficacy of portable Meniett low-pressure pulse generator in Meniere disease. The trial included 129 adults presenting Meniere disease not controlled by conventional medical treatment. The protocol included three phases: 1) placement of a transtympanic tube and evaluation of its effect (with patient was excluded if there was resolution of symptoms); 2) randomization: six-week treatment with Meniett or placebo device; 3) removal of the device and six-week follow-up period. The evaluation criteria were the number of vertigo episodes (at least 20 minutes with a 12-hour free interval) and the impact on daily life as assessed by self-questionnaires. Ninety-seven patients passed to the second phase of the study: 49 and 48 patients received the Meniett or placebo device, respectively. In the placebo group, the number of vertigo episodes decreased from  $4.3 \pm 0.6$  (mean  $\pm$  standard error of the mean) during the first phase to  $2.6 \pm 0.5$  after 6 weeks of treatment, and to  $1.8 \pm 0.8$  after the removal of the device. Similar results were observed in the Meniett device group:  $3.2 \pm 0.4$  episodes during the first phase,  $2.5 \pm$  after 6 weeks of Meniett device treatment, and  $1.5 \pm 0.2$  after the third phase. The authors concluded that an improvement of symptoms was evidenced in all patients, with no difference between the Meniett and the placebo device groups.

Van Sonsbeek et al. (2015) reported on a Cochrane review to assess the effects of positive pressure therapy (e.g., the Meniett device) on the symptoms of Ménière's disease or syndrome. The review included five randomized, clinical trials with 265 participants. Regarding primary outcome, control of vertigo, it was not possible to pool data due to heterogeneity in the measurement of the outcome measures. In most studies, no significant difference was found between the positive pressure therapy group and the placebo group in vertigo scores or vertigo days; one study, at low risk of bias, showed a significant difference in one measure of vertigo control in favor of positive pressure therapy. For the secondary outcomes, statistically significant results for loss



or gain of hearing were found. Hearing was 7.38 decibels better in the placebo group compared to the positive pressure therapy group mean difference (MD) (95% CI 2.51 to 12.25; two studies, 123 participants). The severity of tinnitus and perception of aural fullness were either not measured or inadequate data were provided in the included studies. For the secondary outcome functional level, it was not possible to perform a pooled analysis with one study showing less functional impairment in the positive pressure group than the placebo group; another study did not show any significant results. The authors concluded that there is no evidence, from five included studies, to show that positive pressure therapy is effective for the symptoms of Ménière's disease.

The Meniett device has been evaluated in several small clinical trials (Ahsan et al., 2015; Shojaku, et al., 2011; Dornhoffer, et al., 2008; Mattox, et al., 2008; Gates, et al., 2006; Stokroos, et al., 2006; Boudewyns, et al., 2005; Thomsen, et al., 2005; Gates, et al., 2004; Odkvist, et al., 2000) with the number of study participants ranging from 12-62 persons. Ahsan et al. (2014) reported results of a systematic literature review (eight studies) and meta-analysis (18 studies). Eight studies reported hearing evaluation and improvement in pure tone average after Meniett treatment ( $p=.0085$ ). Data could not be combined for American Academy of Otolaryngology–Head and Neck Surgery functional score due to heterogeneity. Of six studies reporting frequency of vertigo, Meniett treatment significantly reduced frequency of vertigo ( $p<.0001$ ). Limitations of the study include data derived from uncontrolled and retrospective studies, short follow-up of five months, and small numbers of study participants.

In the randomized controlled trial by Thomsen (2005), patients were evaluated for two months to obtain a baseline, after which tympanostomy tubes were placed, followed by two months without treatment to account for the effect of the tympanostomy tubes. Patients then received either the Meniett device for therapy or a sham device that was identical to the active device but did not give any pressure pulses except a slight pressure increase to 2 cm H<sub>2</sub>O for five seconds to maintain the leakage test. The authors state that the patients were unable to detect whether they were using the active or placebo device, but the basis for this statement is not discussed. Patients were evaluated at two, four, and eight weeks of use. Outcomes demonstrated significant improvement in functional level and in patient perception of vertigo in those receiving therapy with the Meniett device compared to the control group. There was a nonstatistically significant trend, toward reduced frequency of vertigo in those using the Meniett device. Study limitations include small population, exclusion of a large number of participants, and the inability to determine whether the improvement is related to placement of the tympanostomy tube itself.

Limitations which limit the ability to translate outcomes to routine use of this device include small study populations, lack of blinding and randomization in the majority of studies, and improvement in outcomes in individuals who were treated with the Meniett device as well as other interventions. Further large, randomized controlled trials are necessary to determine the effectiveness of this device to improve health outcomes.

### **Professional Societies/Organizations**

The Equilibrium Committee of the American Academy of Otolaryngology-Head and Neck Surgery published a Policy Statement on Micropressure Therapy for Ménière's disease (AAO-HNS 2008, updated 2016) noted that there is some medical evidence to support the use of micropressure therapy (such as the Meniett device) in certain cases of Ménière's disease. The therapy can be used as a second level therapy when medical treatment has failed and the device represents a largely non-surgical therapy that should be available as one of the many treatments for Ménière's disease.

### **Use Outside of the US**

No relevant information.

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### **Coding/Billing Information Otolaryngology**

**Note:** 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

### **Otolaryngology Considered Experimental/Investigational/Unproven:**

<b>CPT®*</b> <b>Codes</b>	<b>Description</b>	<b>Comment</b>
<a href="#">0208T</a>	Pure tone audiometry (threshold), automated; air only	
<a href="#">0209T</a>	Pure tone audiometry (threshold), automated; air and bone	
<a href="#">0210T</a>	Speech audiometry threshold, automated;	
<a href="#">0211T</a>	Speech audiometry threshold, automated; with speech recognition	
<a href="#">0212T</a>	Comprehensive audiometry threshold evaluation and speech recognition (0209T, 0211T combined), automated	

<b>HCPCS</b> <b>Codes</b>	<b>Description</b>
<a href="#">E2120</a>	Pulse generator system for tympanic treatment of inner ear endolymphatic fluid



## **Other**

### **Holtranscobalamin Testing (CPT Code 84999)**

Vitamin B12, also known as cobalamin is a water soluble vitamin important in normal neurologic functioning and the formation of red blood cells. Measurement of total serum cobalamin may be used to detect a deficiency state (i.e., <200pg/mL). Sensitivity and specificity of this test is poor in part because serum levels do not always correlate with body stores. Only a portion of cobalamin is metabolically active (i.e., transcobalamin). Transcobalamin-cobalamin complex (i.e., holotranscobalamin or holo-TC) testing has been proposed as an alternative measurement of vitamin B12 deficiency. Testing may be by radio- or enzyme immunoassay.

### **U.S. Food and Drug Administration (FDA)**

In January 2004, the HoloTC RIA device (Axis-Shield Biochemicals, ASA, San Diego, CA) was determined by the FDA to be substantially equivalent as an in-vitro diagnostic assay for quantitative measurement of cobalamin (vitamin B12) bound to the carrier protein transcobalamin in human serum or blood.

### **Literature Review**

Randomized controlled trial (RCT) data are scarce in the published peer-reviewed scientific literature regarding the effectiveness of holotranscobalamin testing for the diagnosis of vitamin B12 deficiency or for use in monitoring response to therapy. Hoey et al (2009) reported results of a systematic review which assessed the effectiveness of biomarkers: vitamin B12, methylmalonic acid and total homocysteine in determining vitamin B12 status in eight RCTs. All studies measured serum and plasma total vitamin B12. All biomarkers were found to be effective measures of altered vitamin B-12 intake in populations with low and borderline baseline vitamin B-12 status ( $p < 0.00001$ ); however, in the case of total vitamin B-12, substantial heterogeneity that could not be fully explained by subgroup analysis was observed. Insufficient data were available to determine the effectiveness of plasma holotranscobalamin, which was measured in only one RCT.

### **Use Outside of the US**

**British Committee for Standards in Hamatology (BCSH):** The BCSH (Devalia, et al., 2014) published recommendations for the diagnosis and treatment of cobalamin and folate disorders. Regarding holtranscobalamin testing, the Committee notes that serum holotranscobalamin has the potential as a first-line test, but an indeterminate grey area may still exist.

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### **Multivariate Analysis of Patient Specific Findings with Quantifiable Computer Probability Assessment (CPT Code 99199)**

Quantitative pretest probability assessment or attribute matching matches an explicit clinical profile of a patient to a reference database to estimate the numeric value for the pretest probability of disease. It has been proposed that this assessment, which is available at the bedside, may aid the health care professional in making the decision to perform certain diagnostic tests.

According to Kline et al. (2010) attribute matching works by a selection process whereby a computer algorithm compares the results of a selected number of predictor variables obtained from the patient being evaluated to a library of research patients previously evaluated for a specific indication compiled from multiple hospitals. The algorithm returns from the library only the "matched" patients who share the same profile of predictor variables as the patient under consideration and reports the proportion of patients with disease in this matched sample.



The PREtestConsult ACS and PREtestConsult PE modules (BreathQuant Medical Systems, Inc., Charlotte, NC) are a software application that estimates the probability of acute coronary syndrome or pulmonary embolism in adult patients. According to information on the PREtestConsult website, clinical data are entered into the modules by means of a personal data assistant or computer.

### **Literature Review**

Randomized controlled clinical data are limited to evaluate the effectiveness and clinical utility of quantifiable computerized probability assessment. Kline et al. (2009) reported the results of a randomized clinical trial involving 400 adult patients (control group, n=185; intervention group, n=184) who were evaluated for chest pain in a single medical center emergency department. Patients had neither obvious evidence for acute coronary syndrome nor other obvious reasons for admission. After an electrocardiogram was performed clinicians were asked to give their estimate of the percentage probability that the patient would have an acute coronary syndrome-defining event in the subsequent 45 days. Randomization was performed by way of a sealed, sequentially numbered envelope that contained assignment to either the control or intervention group. A member of the research team followed the patient to determine physical disposition status from the emergency department. Patients were contacted by telephone at seven and 45 days after enrollment by a research coordinator who was unaware of group assignment. The mean of the pretest probability estimates from the clinicians was 4 (5%) compared with 4 (6%) for the computerized device estimate. Safety and efficacy endpoints for controls versus intervention patients, respectively, were as follows: (1) delayed or missed diagnosis of acute coronary syndrome: 1 of 185 versus 0 of 184, (2) hospital admission with no significant cardiovascular diagnosis: 11% versus 5%, (3) thoracic imaging imparting greater than 5 mSv radiation with a negative result: 20% versus 9%, (4) median length of stay: 11.4 hours versus 9.2 hours, (5) reported feeling "very satisfied" with clinician explanation of problem on follow-up survey: 38% versus 49%, and (6) readmitted within 7 days: 11% versus 4%. Data suggest that use of a quantitative estimate of the pretest probability of acute coronary syndrome was associated with reduced resource use.

### **Use Outside of the US**

No relevant information.

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### **Bioimpedance Spectroscopy to Measure Extracellular Fluid Differences Between Limbs (CPT Code 93702)**

Bioelectrical impedance analysis is a noninvasive technique measures the body's response to electrical current. Current flows along the path of least resistance through the body and thus follows tissues with the highest water content, allowing measurement of edema (AHRQ, 2010). Bioimpedance spectroscopy has been proposed as a tool to detect early stage lymphedema.

Lymphedema is a pathological condition resulting from an accumulation of protein-rich fluid in the interstitial space because of congenital or acquired damage to the lymphatic system. Acquired or secondary lymphedema may be caused by disease, trauma, or an iatrogenic process such as surgery or radiation (Agency for Healthcare Research and Quality [AHRQ], 2010). Lymphedema is generally staged by observation of the individual's physical condition (i.e., stage 0-3) and is typically diagnosed by clinical history and physical examination. AHRQ notes that it is difficult to detect stage 0 or subclinical lymphedema with current methods. According to a



technology assessment by AHRQ (2010) serial measurement of limb volume and or circumference are de facto gold standards for diagnosing secondary edema; however, no single method of assessment has emerged as the standard comparator for randomized clinical trials (AHRQ, 2010).

### **U.S. Food and Drug Administration (FDA)**

Impedimed L-Dex U400 ExtraCellular Fluid analyzer received FDA 510(k) approval on October 3, 2008 with approval of an expansion of indications on November 4, 2011. According to the approval summary it is "indicated for use on adult human patients, utilizing impedance ratios that are displayed as an L-Dex ratio that supports the measurement of extracellular fluid volume between the limbs and is presented to the clinician as an aid to their clinical assessment of unilateral lymphedema of the arm and leg in woman and the leg in men. The device is only indicated for patients who will have or who have had lymph nodes from the axillary and pelvic regions either removed, damaged or irradiated. The device is not intended to diagnose or predict lymphedema of the extremity."

### **Literature Review**

Erdogan et al. (2015) reported on a study of 37 patients with breast cancer who underwent bioimpedance spectroscopy to assess lymphedema. During a one-year follow-up period where investigators used bioimpedance measures, a statistically significant relationship was apparent between the incidence of lymphedema and disease characteristics, including the total number of lymph nodes and the region of radiotherapy. The authors concluded that preliminary results indicate that bioimpedance may be a reasonable method regular monitoring to detect lymphedema. The study was limited by the small subject number and the lack of randomization.

Barrio et al. (2015) reported on a prospective study that compared bioimpedance (L-Dex) and volume displacement (VD) measurements in a prospective cohort of 186 breast cancer patients at risk for lymphedema. Patients received baseline VD and L-Dex; with follow-up measurements performed at three-six months intervals for three years. At each visit, patients fitted into one of three categories: normal (normal VD and L-Dex); abnormal L-Dex (L-Dex > 10 or increase in 10 from baseline and normal VD); or lymphedema (relative arm volume difference of >10 % by VD  $\pm$  abnormal L-Dex). Change in L-Dex was plotted against change in VD; correlation was assessed using the Pearson correlation. At a median follow-up of 18.2 months, 152 patients were normal, 25 had an abnormal L-Dex, and 9 developed lymphedema without a prior L-Dex abnormality. Of the 25 abnormal L-Dex patients, four progressed to lymphedema, for a total of 13 patients with lymphedema. Evaluating all time points, 186 patients had 829 follow-up measurements. Sensitivity and specificity of L-Dex compared with VD were 75 and 93 %, respectively. There was no correlation found between change in VD and change in L-Dex at 3 months ( $r = 0.31$ ) or 6 months ( $r = 0.21$ ). The authors concluded that VD and bioimpedance demonstrated poor correlation with inconsistent overlap of measurements considered abnormal. It was found that of patients with an abnormal L-Dex, few progressed to lymphedema; with most patients with lymphedema not having a prior L-Dex abnormality. The authors noted that further studies are needed to understand the clinical significance of bioimpedance.

Hayes published a technology directory report regarding bioelectrical impedance (bioimpedance) analysis for assessment of lymphedema (Hayes, 2015; 2017). The review included 25 comparative studies, including two randomized controlled trials (RCTs) that assessed the use of bioelectrical impedance analysis (BIA) for detection of lymphedema (LE), with sample sizes of 20 to 295 patients known to have LE or at risk for developing LE. The findings of the report noted that there is insufficient evidence to make conclusive statements regarding the impact of BIA on the detection or assessment of LE. Individual studies or single groups of authors with multiple studies have found moderate to high correlation between BIA, circumferential measurements, and perometry; however, accuracy of BIA varied widely depending on reference standards. It was noted that there was only very limited evidence on clinical utility or the impact of BIA on patient management or outcomes.

Controlled clinical trial data are lacking. Published studies are primarily limited to case series and validation studies. A technology review by AHRQ (2010) notes there is consistent evidence to indicate that lymphedema can be reliably measured using circumferential measurements or volume displacement. Additionally the assessment noted that there is insufficient evidence to draw conclusions about the reliability of other measures including tonometry, ultrasound, lymphoscintigraphy, or bioimpedance. The authors reviewed 41 studies related to diagnosis of lymphedema. In one study included in the technology assessment the test of interest involved



differences in the sum of arm circumference between treated and untreated arms in persons with breast cancer. Circumferential differences to diagnose lymphedema were established at  $\geq 5\text{cm}$  and  $\geq 10\text{cm}$ . For differences of  $\geq 5\text{cm}$  versus bioimpedance, sensitivity was 35% and specificity was 89%. For a difference of  $\geq 10\text{cm}$  versus bioimpedance, sensitivity was 5% and specificity was 100%. For self-report compared to bioimpedance, sensitivity was 65%, specificity was 77%. In another included study bioimpedance was used diagnostically in 102 persons with breast cancer. The sensitivity of bioimpedance compared to limb volume was 10% and specificity was 98%. Two included studies involved bioimpedance alone. The first study found that mean and median bioimpedance measures were greater in the arms of women with lymphedema who survived breast cancer. In the other study single-frequency bioimpedance was highly correlated to bioimpedance spectroscopy ( $r=.99$ ). The authors noted the tests did not drive the choice of treatment or outcome.

### Use Outside of the US

No relevant information.

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### **Near-Infrared Spectroscopy Studies of Lower Extremity Wounds (CPT Code 0493T)**

Foot ulceration remains a major health problem for diabetic patients. A standard method for determining the effectiveness of various treatment methods and quantifying wound healing has not been established. Measurements vary from observer to observer and rely on changes in length, width, and depth (Weingarten, et al., 2010). Treatments can include moist wound healing protocols, offloading to reduce the pressure on the wound, active wound healing agents, and/or active therapies such as hyperbaric oxygen and/or negative pressure therapy. Near-infrared spectroscopy has been proposed as a noninvasive method of measuring the optical properties of tissue oxyhemoglobin content of lower extremity wounds beneath the skin surface to guide treatment.

Diffuse photon density wave (DPDW) methodology of near infrared spectroscopy (NIRS) can be used to measure the absolute concentrations of oxyhemoglobin and deoxyhemoglobin in tissue at depths of up to several centimeters. NIRS utilizes a detector and a dispersive element to allow the intensity at different wavelengths to be recorded. More data are needed to determine the threshold value that will distinguish healing from nonhealing wounds (Niedrauer, 2010).

In this procedure the wound is interrogated using a near-infrared spectroscopy device in up to 10 different locations. Data outputs are in the form of concentrations of oxygenated hemoglobin and total hemoglobin in the blood vessels in the wound. Comparing results on a weekly or biweekly basis, the clinician assesses wound healing progression to determine the need for changes in clinical approach.

### **Literature Review**

Randomized controlled clinical trial data are lacking in the published peer-reviewed scientific literature regarding the safety and effectiveness of near-infrared spectroscopy for the measurement of lower extremity wound healing, including its use for the transcutaneous measurement of oxyhemoglobin. Reisman et al. (2016) reported on a cohort study that examined the use of near-infrared spectroscopy (NIRS) to detect sustained hyperemia following lower extremity trauma. The study examined if NIRS may be a useful monitoring tool for acute compartment syndrome (ACS). Expected normal values for this measurement have yet to be established. The study included 25 cases with acute unilateral lower extremity fractures. NIRS measurements for hemoglobin saturated with oxygen (rSO<sub>2</sub>) were taken approximately 48 hours after surgical stabilization for each compartment bilaterally, using the contralateral (uninjured) leg as an internal control. Mean rSO<sub>2</sub> values taken 48 hours from surgical stabilization from each compartment of the patients' injured legs were significantly higher than the mean values of the contralateral legs (injured = 70, 68, 72, 70; contralateral = 55, 54, 57, 56 for anterior, lateral, deep posterior, and superficial posterior compartments, respectively;  $p < 0.0001$  for all compartments). The study was limited by the lack of randomization and small subject number.

### **Use Outside of the US**

No relevant information.

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### **MarginProbe® (CPT Code 19499)**



The MarginProbe System technology is based on the principle of radiofrequency (RF) spectroscopy. The technology relies on subjecting tissue to an electric field, and then measuring the tissue response to that field, yielding an electromagnetic signature. According to the manufacturer, the surgeon applies external fields to suspect tissue and captures minute differences in electromagnetic properties. The system compares those responses to an internal database of known signatures in healthy and cancerous tissues (Dune Medical, 2015).

#### **U. S. Food and Drug Administration**

In December 27, 2012, MarginProbe® (Dune Medical Devices Inc., Paoli, PA, formerly Farmington, MA) received PMA approval from the Food and Drug Administration (FDA). The Dune MarginProbe®™ System is an adjunctive diagnostic tool for identification of cancerous tissue at the margins ( $\leq 1\text{mm}$ ) of the main ex-vivo lumpectomy specimen following primary excision and is indicated for intraoperative use in conjunction with standard methods (such as intraoperative imaging and palpation) for patients undergoing lumpectomy for previously diagnosed breast cancer.

#### **Literature Review**

Hayes published a health technology brief regarding the MarginProbe System (Dune Medical Devices) (Hayes, 2017). The review included seven studies ( $n=42$  to 596) that evaluated the clinical validity, utility, and safety of MarginProbe for intraoperative assessment of surgical margins in patients with breast cancer. Two studies were randomized controlled trials (RCTs), 3 were nonrandomized cohort studies with historical controls, and 2 were prospective cohort studies. One study was determined to be fair quality; four poor quality; and, two of very poor quality. Across studies, the rates of re-excision were statistically significantly lower in patients managed using MarginProbe plus standard of care (SOC) methods when compared with SOC methods alone. While most studies focused on rates of re-excision in patients with positive tumor margins, a critical endpoint—local tumor recurrence—was not evaluated in any study, which precludes any conclusions regarding the impact of the device on clinical oncologic outcomes. Moderate margin-level sensitivity (range, 70% to 75.2%) and low-to-moderate specificity (range, 46.4% to 70%) implies that positive margins could be missed by the device or that healthy tissue could be unnecessarily resected. The review noted study limitations included: use of historical controls; short duration of follow-up; failure to standardize methods used preoperatively to locate nonpalpable lesions; failure to standardize surgical methods and SOC methods to assess specimen margins across study arms; and failure to assess clinically relevant oncologic outcomes such as local recurrence or cancer-free survival rates. Additional studies are needed to determine whether MarginProbe is a useful adjunct to SOC methods for intraoperative margin assessment of breast tumors.

Randomized controlled clinical trial data are limited in the published, peer-reviewed scientific literature. Data are primarily in the form of prospective case controlled and retrospective analyses.

Sebastian et al. (2015) reported on a retrospective, observational study that provided compilation of data from routine use of the device, to assess the impact of device utilization on re-excision rates on groups of consecutive patients, before and after the implementation of intraoperative use of the device during lumpectomy procedures. Historical re-excision rates for each surgeon (four surgeons in three centers) were established based on a consecutive set of patients from a time period proximal to initiation of use of the device. In total, 165 cases lumpectomy cases were performed. Positive margins resulted in additional re-excision procedures in 9.7% (16/165) of the cases. The corresponding historical set from 2012 and 2013 consisted of 186 lumpectomy cases, in which additional re-excision procedures were performed in 25.8% (48/186) of the cases. The reduction in the rate of re-excision procedures was significant 62% ( $P < 0.0001$ ). This study is limited by the retrospective nature of the study and small sample size.

Schnabel et al. (2014) published results of a randomized prospective clinical trial evaluating lumpectomy margin assessment with the use of MarginProbe in addition to standard methods in 596 patients with nonpalpable breast malignancies. In the device arm, MarginProbe was used to examine the main lumpectomy specimens and direct additional excision of positive margins. Intraoperative imaging was used in both arms; no intraoperative pathology assessment was permitted. False-negative rates were 24.8 and 66.1 % and false-positive rates were 53.6 and 16.6 % in the device and control arms, respectively. In similar proportions of patients in both arms, the main lumpectomy specimen contained at least one positive margin. In patients with positive margins on initial lumpectomy specimens, an average of two margins was involved, with no difference between the two arms. Surgeons correctly identified all positive margins on the main specimen and removed additional tissue from



those involved margins in 33 of 147 cases (22 %) in the control arm, versus 101 of 163 (62 %) cases in the device arm ( $p < 0.0001$ ). 19.8 % of patients in the device arm underwent second procedures for reexcision of lumpectomy margins compared with 25.8 % of patients in the control arm, representing a 6 % absolute (23 % relative) reduction associated with MarginProbe use. With regard to reexcision procedures that were required because of positive margins originating from the main lumpectomy specimens the control arm rate was 20.8 % compared with 10.0 % in the device arm ( $p = 0.002$ ). Study limitations included that this study did not test whether the device would allow for less surgery to be performed if the specimens were carefully examined intraoperatively by pathologists, with or without the selective use of frozen section. Although results are promising, additional large randomized trials and consensus support by way of published society/professional organization are necessary before this device can be considered standard of care.

Thill et al. (2014) assessed the benefit of MarginProbe in intraoperative margin assessment during breast conservation surgery (BCS) of ductal carcinoma in situ, the associated reduction of re-excisions and the cosmetic outcome in 42 patients. The study was a multi-center, single arm, post market study enrolling 55 patients and was conducted at three sites in Germany. During the study MarginProbe was used as an adjunctive tool to standard of care. Results were compared to a historical re-excision rate, defined as the number of re-excisions (26/67 patients, 39%) that had been performed on DCIS patients from the general screening. The device use was associated with a reduction in re-excision rates by 56%, from 39% to 17% ( $p = 0.018$ ). In 21% (9/42) of the cases use of the device led to a direct conversion to mastectomy due to extensive disease identified, sparing an additional re-excision BCS. Study limitations include small number of participants and uncontrolled study design.

Allweis et al. (2008) reported results of a randomized clinical trial in 300 patients (device:  $n = 149$ , control:  $n = 151$ ) assessing a real-time, intraoperative probe for positive margin detection in breast-conserving surgery. In the device group, the probe was applied to the lumpectomy specimen and additional tissue was excised according to device readings. Study arms were compared by reoperation rates and by correct surgical reaction confirmed by histology. In both arms surgeons were allowed to use any standard of care (SOC) intraoperative methods to evaluate margin status such as palpation, specimen imaging, and intraoperative gross and/or microscopic pathology assessment. Pathology data were collected for the primary lumpectomy and all repeat ipsilateral surgical procedures within 6 months. The device was only applied to the main lumpectomy specimen and was not used in reoperations. Reoperation rate between the two groups was not statically significant ( $p = 0.98$ ). The proportion of patients with long-term "excellent" or "good" cosmetic evaluation was similar in both arms (71% and 69% for the two groups, respectively ( $p = 0.71$ )). Data do not suggest improved reoperation rates compared to control.

#### **Use Outside of the US**

No relevant information

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**Optical Coherence Tomography of Breast or Axillary Lymph Node (CPT Codes 0351T, 0352T, 0353T, 0354T)**

Optical coherence tomography (OCT) is a high-resolution, near-infrared light imaging modality that has been proposed as a non-surgical method of assessing breast and axillary lymph node margins.

**Literature Review**

Randomized clinical trial data are lacking in the published, peer-reviewed scientific literature. Butler-Henderson et al. (2014) published a systemic review of 27 studies examining current intraoperative methods for assessing margin status. The final pathology status, statistical measures including accuracy of tumor margin assessment, average time impact on the procedure and second operation rate, were used as criteria for comparison between studies. One third (9/27) of the studies recruited subjects prospectively but did not act on results from intraoperative methods of assessment (IMA), (i.e. prospective observational). About 40% (11/27) of studies also recruited prospectively and acted on IMA results, (i.e. prospective experimental), whereas the remaining (7/27) studies were retrospective chart reviews. Overall, accuracy of IMA was well reported. Accuracy rates for ultrasound, frozen section and optical coherence tomography were 99.6%, 98.02% and 90%, respectively. Imprint cytology had a sensitivity of 80-85% and specificity of 85-100%. Optical coherence tomography reported a sensitivity of 100% and specificity of 82%, but average operation time was unavailable. Only one study examined the use of optical coherence tomography in breast cancer surgery. Additional operation time and second operation rate were not investigated. The authors note that caution is necessary before making any recommendation concerning its use in breast surgery.

Nguyen et al. (2009) reported results of a prospective, observational study. OCT demonstrated a sensitivity of 100% and specificity of 82% for OCT as a real-time method for margin assessment during breast-conserving surgery involving a total of 37 patients. OCT images were acquired from surgical margins of lumpectomy samples. Histologic findings identified nine true positives, nine true negatives, two false positives and no false negatives. The authors concluded that OCT shows potential as a real-time method for intraoperative margin assessment in breast-conserving surgeries. Study limitations include nonrandomized design and small sample size.

**References**

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2. Butler-Henderson K, Lee AH, Price RI, Waring K. Intraoperative assessment of margins in breast conserving therapy: a systematic review. *Breast*. 2014 Apr;23(2):112-9.
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**Coding/Billing Information Other**

**Note:** 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

**Considered Experimental/Investigational/Unproven when used to report Margin Probe®:**

CPT®*	Description	Comment
<a href="#">19499</a>	Unlisted procedure, breast	Considered Experimental/Investigational/Unproven when used to report MarginProbe®



**Considered Experimental/Investigational/Unproven when used to report multivariate analysis of patient specific findings with quantifiable computer probability assessment:**

<b>CPT®* Codes</b>	<b>Description</b>	<b>Comment</b>
<a href="#">99199</a>	Unlisted special service, procedure or report	Considered Experimental/Investigational/Unproven when used to report multivariate analysis of patient specific findings with quantifiable computer probability assessment

**Other Services Considered Experimental/Investigational/Unproven:**

<b>CPT®* Codes</b>	<b>Description</b>	<b>Comment</b>
<a href="#">84999</a>	Unlisted chemistry procedure	Considered Experimental/Investigational/Unproven when used to report Holotranscobalamin, quantitative (Holotranscobalamin Testing)
<a href="#">93702</a>	Bioimpedance spectroscopy (BIS), extracellular fluid analysis for lymphedema assessment(s)	
<a href="#">0351T</a>	Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; real-time intraoperative	
<a href="#">0352T</a>	Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; interpretation and report, real-time or referred	
<a href="#">0353T</a>	Optical coherence tomography of breast, surgical cavity; real-time intraoperative	
<a href="#">0354T</a>	Optical coherence tomography of breast, surgical cavity; interpretation and report, real-time or referred	
<a href="#">0493T</a>	Near-infrared spectroscopy studies of lower extremity wounds (eg, for oxyhemoglobin measurement)	

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## Coding/Billing Information

**Note:** 1) This list of codes may not be all-inclusive.  
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

### **Anoscopy, High Resolution (HRA)**

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

<b>CPT®* Codes</b>	<b>Description</b>
<a href="#">46601</a>	Anoscopy; diagnostic, with high-resolution magnification (HRA) (eg, colposcope, operating microscope) and chemical agent enhancement, including collection of specimen(s) by brushing or washing, when performed



<a href="#">46607</a>	Anoscopy; with high-resolution magnification (HRA) (eg, colposcope, operating microscope) and chemical agent enhancement, with biopsy, single or multiple
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#### **Whole Body or Selective Head Therapeutic Hypothermia**

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

<b>CPT®* Codes</b>	<b>Description</b>
<a href="#">99184</a>	Initiation of selective head or total body hypothermia in the critically ill neonate, includes appropriate patient selection by review of clinical, imaging and laboratory data, confirmation of esophageal temperature probe location, evaluation of amplitude EEG, supervision of controlled hypothermia, and assessment of patient tolerance of cooling

#### **Tumor Treatment Fields (TTF) Therapy (i.e., Optune™)**

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

<b>HCPCS Codes</b>	<b>Description</b>
<a href="#">A4555</a>	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
<a href="#">E0766</a>	Electrical stimulation device used for cancer treatment, includes all accessories, any type

**Considered Experimental/Investigational/Unproven when used to report treatment planning software (i.e., NovoTAL) for use with tumor treatment fields:**

<b>CPT®* Codes</b>	<b>Description</b>	<b>Comment</b>
<a href="#">64999</a>	Unlisted procedure, nervous system	Considered Experimental/Investigational/Unproven when used to report treatment planning software (i.e., NovoTAL) for use with tumor treatment fields

#### **Insertion of Ocular Telescope Prosthesis Including Crystalline Lens**

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

<b>CPT®* Codes</b>	<b>Description</b>
<a href="#">0308T</a>	Insertion of ocular telescope prosthesis including removal of crystalline lens or intraocular lens prosthesis

<b>HCPCS Codes</b>	<b>Description</b>
<a href="#">C1840</a>	Lens, intraocular (telescopic)

#### **Margin Probe®**

**Considered Experimental/Investigational/Unproven when used to report Margin Probe®:**

<b>CPT®*</b>	<b>Description</b>	<b>Comment</b>
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<b>Codes</b>		
<a href="#">19499</a>	Unlisted procedure, breast	Considered Experimental/Investigational/Unproven when used to report anoscopy with delivery of thermal energy to the muscle of the anal canal when used to report Margin Probe®

#### **Multivariate Analysis of Patient Specific Findings with Quantifiable Computer Probability Assessment**

**Considered Experimental/Investigational/Unproven when used to report multivariate analysis of patient specific findings with quantifiable computer probability assessment:**

<b>CPT® Codes</b>	<b>Description</b>	<b>Comment</b>
<a href="#">99199</a>	Unlisted special service, procedure or report	Considered Experimental/Investigational/Unproven when used to report multivariate analysis of patient specific findings with quantifiable computer probability assessment

#### **Suprachoroidal and Extrascleral Placement of Pharmacologic Agent**

**Considered Experimental/Investigational/Unproven when used to report suprachoroidal delivery of pharmacologic agent or conjunctival incision with posterior extrascleral placement of pharmacologic agent:**

<b>CPT® Codes</b>	<b>Description</b>	<b>Comment</b>
<a href="#">67299</a>	Unlisted procedure, posterior segment	Considered Experimental/Investigational/Unproven when used to report suprachoroidal delivery of pharmacologic agent
<a href="#">68399</a>	Unlisted procedure, conjunctiva	Considered Experimental/Investigational/Unproven when used to report conjunctival incision with posterior extrascleral placement of a pharmacologic agent
<a href="#">0465T</a>	Suprachoroidal injection of a pharmacologic agent (does not include supply of medication)	

#### **Additional Services Considered Experimental/Investigational/Unproven:**

<b>CPT® Codes</b>	<b>Description</b>	<b>Comment</b>
<a href="#">32994</a>	Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging	



	guidance when performed, unilateral; cryoablation	
<a href="#">33340</a>	Percutaneous transcatheter closure of the left atrial appendage with endocardial implant, including fluoroscopy, transseptal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, when performed, and radiological supervision and interpretation	
<a href="#">34806</a>	Transcatheter placement of wireless physiologic sensor in aneurysmal sac during endovascular repair, including radiological supervision and interpretation, instrument calibration, and collection of pressure data (List separately in addition to code for primary procedure) (Code deleted 12/31/2017)	
<a href="#">34839</a>	Physician planning of a patient-specific fenestrated visceral aortic endograft requiring a minimum of 90 minutes of physician time	
<a href="#">34841</a>	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including one visceral artery endoprosthesis (superior mesenteric, celiac or renal artery)	
<a href="#">34842</a>	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including two visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
<a href="#">34843</a>	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including three visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
<a href="#">34844</a>	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including four or more visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
<a href="#">34845</a>	Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including one visceral artery endoprosthesis (superior mesenteric,	



	celiac or renal artery)	
<a href="#">34846</a>	Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including two visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
<a href="#">34847</a>	Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including three visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
<a href="#">34848</a>	Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including four or more visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])	
<a href="#">46999</a>	Unlisted procedure, anus	Considered Experimental/Investigational/Unproven when used to report transanal radiofrequency therapy for fecal Incontinence (e.g., SECCA procedure)
<a href="#">58674</a>	Laparoscopy, surgical, ablation of uterine fibroid(s) including intraoperative ultrasound guidance and monitoring, radiofrequency	
<a href="#">64999</a>	Unlisted procedure, nervous system	Considered Experimental/Investigational/Unproven when used to report implantation of trial or permanent electrode arrays or pulse generators for peripheral subcutaneous field stimulation
<a href="#">83993</a>	Calprotectin, fecal	
<a href="#">84999</a>	Unlisted chemistry procedure	Considered Experimental/Investigational/Unproven when used to report Holotranscobalamin, quantitative (Holtranscobalamin Testing)
<a href="#">88749</a>	Unlisted in vivo (eg, transcutaneous) laboratory service	Considered Experimental/Investigational/



		Unproven when used to report skin advanced glycation endproducts measurement by multi-wavelength fluorescent spectroscopy
<a href="#">91112</a>	Gastrointestinal transit and pressure measurement, stomach through colon, wireless capsule, with interpretation and report	
<a href="#">91299</a>	Unlisted diagnostic gastroenterology procedure	Considered Experimental/Investigational/Unproven when used to report 13C-Spirulina Gastric Emptying Breath Test (GEBT)
<a href="#">92978</a>	Endoluminal imaging of coronary vessel or graft using intravascular (IVUS) or optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; initial vessel (List separately in addition to code for primary procedure)	Considered Experimental/Investigational/Unproven when used to report CPT code 92978 using endoluminal imaging of coronary vessel or graft using optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; initial vessel
<a href="#">92979</a>	Endoluminal imaging of coronary vessel or graft using intravascular (IVUS) or optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; each additional vessel (List separately in addition to code for primary procedure)	Considered Experimental/Investigational/Unproven when used to report CPT code 92979 using endoluminal imaging of coronary vessel or graft using optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; each additional vessel
<a href="#">93702</a>	Bioimpedance spectroscopy (BIS), extracellular fluid analysis for lymphedema assessment(s)	
<a href="#">93799</a>	Unlisted cardiovascular service or procedure	Considered Experimental/Investigational/Unproven when used to report acoustic cardiography
<a href="#">93982</a>	Noninvasive physiologic study of implanted wireless pressure sensor in aneurysmal sac following endovascular repair, complete study including recording, analysis of pressure and waveform tracings, interpretation and report	
<a href="#">94799</a>	Unlisted pulmonary service or procedure	Considered Experimental/Investigational/Unproven when used to report intermittent



		measurement of wheeze rate for bronchodilator or bronchial challenge diagnostic evaluation
<a href="#">95999</a>	Unlisted neurological or neuromuscular diagnostic procedure	Considered Experimental/Investigational/Unproven when used to report tremor measurement with accelerometer(s) and/or gyroscope(s)
<a href="#">99199</a>	Unlisted special service, procedure or report	Considered Experimental/Investigational/Unproven when used to report near-infrared guidance for vascular access requiring real-time digital visualization of subcutaneous vasculature for evaluation of potential access sites and vessel patency
<a href="#">0100T</a>	Placement of a subconjunctival retinal prosthesis receiver and pulse generator, and implantation of intra-ocular retinal electrode array, with vitrectomy	
<a href="#">0106T</a>	Quantitative sensory testing (QST), testing and interpretation per extremity; using touch pressure stimuli to assess large diameter sensation	
<a href="#">0107T</a>	Quantitative sensory testing (QST), testing and interpretation per extremity; using vibration stimuli to assess large diameter fiber sensation	
<a href="#">0108T</a>	Quantitative sensory testing (QST), testing and interpretation per extremity; using cooling stimuli to assess small nerve fiber sensation and hyperalgesia	
<a href="#">0109T</a>	Quantitative sensory testing (QST), testing and interpretation per extremity; using heat-pain stimuli to assess small nerve fiber sensation and hyperalgesia	
<a href="#">0110T</a>	Quantitative sensory testing (QST), testing and interpretation per extremity; using other stimuli to assess sensation	
<a href="#">0174T</a>	Computer aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed concurrent with primary interpretation (List separately in addition to code for primary procedure)	
<a href="#">0175T</a>	Computer aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed remote from primary interpretation	
<a href="#">0190T</a>	Placement of intraocular radiation source applicator (List separately in addition to primary procedure)	
<a href="#">0205T</a>	Intravascular catheter-based coronary vessel or graft spectroscopy (eg, infrared) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation, and report, each vessel (List separately in addition to primary procedure)	



<a href="#">0207T</a>	Evacuation of meibomian glands, automated, using heat and intermittent pressure, unilateral	
<a href="#">0208T</a>	Pure tone audiometry (threshold), automated; air only	
<a href="#">0209T</a>	Pure tone audiometry (threshold), automated; air and bone	
<a href="#">0210T</a>	Speech audiometry threshold, automated	
<a href="#">0211T</a>	Speech audiometry threshold, automated with speech recognition	
<a href="#">0212T</a>	Comprehensive audiometry threshold evaluation and speech recognition (0209T, 0211T combined), automated	
<a href="#">0234T</a>	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; renal artery	
<a href="#">0235T</a>	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; visceral artery (except renal), each vessel	
<a href="#">0236T</a>	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; abdominal aorta	
<a href="#">0237T</a>	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; brachiocephalic trunk and branches, each vessel	
<a href="#">0238T</a>	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; iliac artery, each vessel	
<a href="#">0254T</a>	Endovascular repair of iliac artery bifurcation (eg, aneurysm, pseudoaneurysm, arteriovenous malformation, trauma, dissection) using bifurcated endograft from the common iliac artery into both the external and internal iliac artery, including all selective and/or nonselective catheterization(s) required for device placement and all associated radiological supervision and interpretation, unilateral	
<a href="#">0255T</a>	Endovascular repair of iliac artery bifurcation (eg, aneurysm, pseudoaneurysm, arteriovenous malformation, trauma) using bifurcated endoprosthesis from the common iliac artery into both the external and internal iliac artery, unilateral; radiological supervision and interpretation (Code deleted 12/31/2017)	
<a href="#">0266T</a>	Implantation or replacement of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intraoperative interrogation, programming, and repositioning, when performed)	
<a href="#">0267T</a>	Implantation or replacement of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming and repositioning, when performed)	
<a href="#">0268T</a>	Implantation or replacement of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)	
<a href="#">0269T</a>	Revision or removal of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)	
<a href="#">0270T</a>	Revision or removal of carotid sinus baroreflex activation	



	device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)	
<a href="#">0271T</a>	Revision or removal of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)	
<a href="#">0272T</a>	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (eg, battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day);	
<a href="#">0273T</a>	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (eg, battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day); with programming	
<a href="#">0293T</a>	Insertion of left atrial hemodynamic monitor; complete system, includes implanted communication module and pressure sensor lead in left atrium including transseptal access, radiological supervision and interpretation, and associated injection procedures, when performed (Code deleted 12/31/2017)	
<a href="#">0294T</a>	Insertion of left atrial hemodynamic monitor; pressure sensor lead at time of insertion of pacing cardioverter-defibrillator pulse generator including radiological supervision and interpretation and associated injection procedures, when performed (List separately in addition to primary procedure) (Code deleted 12/31/2017)	
<a href="#">0337T</a>	Endothelial function assessment, using peripheral vascular response to reactive hyperemia, non-invasive (eg, brachial artery ultrasound, peripheral artery tonometry), unilateral or bilateral	
<a href="#">0338T</a>	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; unilateral	
<a href="#">0339T</a>	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; bilateral	
<a href="#">0340T</a>	Ablation, pulmonary tumor(s), including pleura or chest wall when involved by tumor extension, percutaneous, cryoablation, unilateral, includes imaging guidance (Code	



	deleted 12/31/2017)	
<a href="#">0341T</a>	Quantitative pupillometry with interpretation and report, unilateral or bilateral	
<a href="#">0342T</a>	Therapeutic apheresis with selective HDL delipidation and plasma reinfusion	
<a href="#">0351T</a>	Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; real-time intraoperative	
<a href="#">0352T</a>	Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; interpretation and report, real-time or referred	
<a href="#">0353T</a>	Optical coherence tomography of breast, surgical cavity; real-time intraoperative	
<a href="#">0354T</a>	Optical coherence tomography of breast, surgical cavity; interpretation and report, real-time or referred	
<a href="#">0378T</a>	Visual field assessment, with concurrent real time data analysis and accessible data storage with patient initiated data transmitted to a remote surveillance center for up to 30 days; review and interpretation with report by a physician or other qualified health care professional	
<a href="#">0379T</a>	Visual field assessment, with concurrent real time data analysis and accessible data storage with patient initiated data transmitted to a remote surveillance center for up to 30 days; technical support and patient instructions, surveillance, analysis, and transmission of daily and emergent data reports as prescribed by a physician or other qualified health care professional	
<a href="#">0380T</a>	Computer-aided animation and analysis of time series retinal images for the monitoring of disease progression, unilateral or bilateral, with interpretation and report	
<a href="#">0381T</a>	External heart rate and 3-axis accelerometer data recording up to 14 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional	
<a href="#">0382T</a>	External heart rate and 3-axis accelerometer data recording up to 14 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only	
<a href="#">0383T</a>	External heart rate and 3-axis accelerometer data recording from 15 to 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional	
<a href="#">0384T</a>	External heart rate and 3-axis accelerometer data recording from 15 to 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only	
<a href="#">0385T</a>	External heart rate and 3-axis accelerometer data recording more than 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician	



	or other qualified health care professional	
<a href="#">0386T</a>	External heart rate and 3-axis accelerometer data recording more than 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only	
<a href="#">0397T</a>	Endoscopic retrograde cholangiopancreatography (ERCP), with optical endomicroscopy (List separately in addition to code for primary procedure)	
<a href="#">0404T</a>	Transcervical uterine fibroid(s) ablation with ultrasound guidance, radiofrequency	
<a href="#">0408T</a>	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator with transvenous electrodes	
<a href="#">0409T</a>	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator only	
<a href="#">0410T</a>	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; atrial electrode only	
<a href="#">0411T</a>	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; ventricular electrode only	
<a href="#">0412T</a>	Removal of permanent cardiac contractility modulation system; pulse generator only	
<a href="#">0413T</a>	Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular)	
<a href="#">0414T</a>	Removal and replacement of permanent cardiac contractility modulation system pulse generator only	
<a href="#">0415T</a>	Repositioning of previously implanted cardiac contractility modulation transvenous electrode, (atrial or ventricular lead)	
<a href="#">0416T</a>	Relocation of skin pocket for implanted cardiac contractility modulation pulse generator	
<a href="#">0417T</a>	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, implantable cardiac contractility modulation system	
<a href="#">0418T</a>	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter; implantable cardiac contractility modulation system	

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## PROVIDER POLICIES & PROCEDURES

### ELECTRIC TUMOR TREATMENT FIELD THERAPY (E.G. OPTUNE DEVICE)

The purpose of this document is to assist providers enrolled in the Connecticut Medical Assistance Program (CMAP) with the information needed to support a medical necessity determination for electric tumor treatment field therapy. By clarifying the information needed for prior authorization of services, HUSKY Health hopes to facilitate timely review of requests so that individuals obtain the medically necessary care they need as quickly as possible.

Tumor treatment field (TTF) therapy uses a noninvasive device to create alternating, wave-like electric fields to selectively disrupt mitosis in dividing cancer cells. TTF is approved for use in the treatment of glioblastoma multiforme (GBM), the most prevalent and primary malignant brain tumor in adults. The device is comprised of an electric field generator, a connection cable and box, transducer arrays, and batteries along with a charger, power supply and carrying bag. The transducer arrays are directly applied to the scalp and must be changed at least two times per week. The device is portable for use in normal daily activities and is typically worn for at least 18 hours per day.

#### CLINICAL GUIDELINE

Coverage guidelines for TTF therapy are made in accordance with the Department of Social Services (DSS) definition of Medical Necessity. The following criteria are guidelines only. Coverage determinations are based on an assessment of the individual and their clinical needs. If the guidelines conflict with the definition of Medical Necessity, the definition of Medical Necessity shall prevail. The guidelines are as follows:

Use of a device to generate TTF is generally considered medically necessary for adults (at least 22 years of age) with histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma) when used:

1. As monotherapy:
  - A. Following histologically or radiologically confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy; and
  - B. When intended as an alternative to standard medical therapy after surgical and radiation options have been exhausted; **OR**
2. As adjunctive therapy with temozolomide for newly-diagnosed histologically confirmed supratentorial glioblastoma following debulking surgery and completion of radiation therapy together with concomitant standard chemotherapy.

#### Initial Coverage

When all of the above criteria are met, an initial 3 months of TTF therapy will be approved.

#### Continuing Coverage:

In addition to meeting the above criteria, subsequent approval(s) for continuation of TTF therapy is based on:

1. Evidence of no documented disease progression by MRI or if MRI contraindicated, as evidenced by clinical re-evaluation; and

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2. Documentation that the individual has been wearing the device for at least 18 hours per day.

The use of a device to generate TTF is generally considered investigational and therefore not medically necessary for the treatment of other malignant tumors (e.g., breast, lung, melanoma, ovarian cancer, pancreatic cancer and solid tumor brain metastases) and for all other indications because the effectiveness has not been established.

The use of combined TTF therapy and chemo-immuno therapy other than temozolomide for the treatment of other malignant tumors is generally considered investigational and therefore not medically necessary because the effectiveness of this approach has not been established.

**NOTE: EPSDT Special Provision**

Early and Periodic Screening, Diagnosis, and Treatment (EPSDT) is a federal Medicaid requirement that requires the Connecticut Medical Assistance Program (CMAP) to cover services, products, or procedures for Medicaid enrollees under 21 years of age where the service or good is medically necessary health care to correct or ameliorate a defect, physical or mental illness, or a condition identified through a screening examination. The applicable definition of medical necessity is set forth in Conn. Gen. Stat. Section 17b-259b (2011) [ref. CMAP Provider Bulletin PB 2011-36].

**PROCEDURE**

Prior authorization for TTF therapy is required. Coverage determinations will be based upon a review of requested and/or submitted case-specific information.

**The following information is needed to review requests for TTF therapy:**

1. Fully completed Outpatient Prior Authorization Request Form or fully completed authorization request via on-line web portal;
2. A prescription from a licensed physician enrolled in the Connecticut Medical Assistance Program (CMAP);
3. Clinical information supporting the medical necessity of the treatment;
4. Pricing information\*;
5. Results of follow-up MRI or clinical re-evaluation (when requesting continuing coverage);
6. Documentation that the individual has been wearing the device for at least 18 hours per day (when requesting continuing coverage); and
7. Other information as requested.

\* Reimbursed at MSRP – 15%. Payment includes all necessary goods and services related to TTF therapy.

**EFFECTIVE DATE**

This Policy is effective for prior authorization requests for TTF therapy for individuals covered under the HUSKY Health Program beginning November 1, 2017.

**LIMITATIONS**

N/A

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**CODE:**

Code	Description
E1399	Durable medical equipment, miscellaneous

**DEFINITIONS**

1. **HUSKY A:** Connecticut children and their parents or a relative caregiver; and pregnant women may qualify for HUSKY A (also known as Medicaid). Income limits apply.
2. **HUSKY B:** Uninsured children under the age of 19 in higher income households may be eligible for HUSKY B (also known as the Children's Health Insurance Program) depending on their family income level. Family cost-sharing may apply.
3. **HUSKY C:** Connecticut residents who are age 65 or older or residents who are ages 18-64 and who are blind, or have another disability, may qualify for Medicaid coverage under HUSKY C (this includes Medicaid for Employees with Disabilities (MED-Connect), if working). Income and asset limits apply.
4. **HUSKY D:** Connecticut residents who are ages 19-64 without dependent children and who: (1) do not qualify for HUSKY A; (2) do not receive Medicare; and (3) are not pregnant, may qualify for HUSKY D (also known as Medicaid for the Lowest-Income populations).
5. **HUSKY Health Program:** The HUSKY A, HUSKY B, HUSKY C, HUSKY D and HUSKY Limited Benefit programs, collectively.
6. **HUSKY Limited Benefit Program or HUSKY, LBP:** Connecticut's implementation of limited health insurance coverage under Medicaid for individuals with tuberculosis or for family planning purposes and such coverage is substantially less than the full Medicaid coverage.
7. **Medically Necessary or Medical Necessity:** (as defined in Connecticut General Statutes § 17b-259b) Those health services required to prevent, identify, diagnose, treat, rehabilitate or ameliorate an individual's medical condition, including mental illness, or its effects, in order to attain or maintain the individual's achievable health and independent functioning provided such services are: (1) Consistent with generally-accepted standards of medical practice that are defined as standards that are based on (A) credible scientific evidence published in peer-reviewed medical literature that is generally recognized by the relevant medical community, (B) recommendations of a physician-specialty society, (C) the views of physicians practicing in relevant clinical areas, and (D) any other relevant factors; (2) clinically appropriate in terms of type, frequency, timing, site, extent and duration and considered effective for the individual's illness, injury or disease; (3) not primarily for the convenience of the individual, the individual's health care provider or other health care providers; (4) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the individual's illness, injury or disease; and (5) based on an assessment of the individual and his or her medical condition.
8. **Prior Authorization:** A process for approving covered services prior to the delivery of the service or initiation of the plan of care based on a determination by CHNCT as to whether the requested service is medically necessary.

**RESOURCES AND REFERENCES:****Government Agency, Medical Society and Other Authoritative Publications:**

- Centers for Medicare and Medicaid Services (CMS), Health Care Procedural Coding System Level II Manual: 2017
- CGS Administrators, LLC. Local Coverage Determination (LCD) for Tumor Treatment Field

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- Kirson ED, Schneiderman RS, Dbaly V, et al. Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields). BMC Med Phys. 2009;9:1
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## PUBLICATION HISTORY

Status	Date	Action Taken
Original Publication	September, 2017	Approved at the July 26, 2017 Medical Policy Review Committee meeting. Approved by the Clinical Quality Subcommittee on September 21, 2017. Approved by DSS on September 26, 2017.

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# MEDICAL POLICY

**SUBJECT: TUMOR-TREATMENT FIELD THERAPY  
FOR GLIOBLASTOMA**

**EFFECTIVE DATE: 05/28/15  
REVISED DATE: 08/18/16**

**POLICY NUMBER: 6.01.45**

**CATEGORY: Technology Assessment**

**PAGE: 1 OF: 5**

- *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.*
- *If a commercial product, including an Essential Plan product, covers a specific service, medical policy criteria apply to the benefit.*
- *If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.*

## **POLICY STATEMENT:**

- I. Based upon our criteria and assessment of peer-reviewed literature, Tumor-Treatment Field (TTF) therapy using the NovoTTF-100A™ System for treatment of recurrent Glioblastoma multiforme (GBM) is considered **medically appropriate** when all of the following criteria have been met:
  - A. 1<sup>st</sup> or 2<sup>nd</sup> recurrence of GBM; and
  - B. The individual has a Karnofsky Performance Status (KPS) of 90 or greater; and
  - C. The individual has not received prior treatment with Bevacizumab; and
  - D. The device is to be used as monotherapy after failure of standard medical therapy (e.g., chemotherapy, surgery, and radiation therapy).
  - E. There is documented evidence the member is compliant with the TTF device during a one month trial period. Compliance is defined as use of the device for 18 hours or more per day during the one month trial period.
- II. Based upon our criteria and assessment of peer-reviewed literature, Tumor-Treatment Field (TTF) therapy using the NovoTTF-100A™ System for treatment of newly diagnosed Glioblastoma multiforme (GBM) is considered **medically appropriate** when the following criteria have been met:
  - A. The device is to be used as an adjunct with the chemotherapy drug temozolomide (TMZ); and
  - B. Following standard treatments that include maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

## **POLICY GUIDELINES:**

- I. The NovoTTF-100A™ System will be allowable for up to 6 months if the patient is compliant with the regimen. Continued use after 6 months will require additional documentation to show no progression in the patient's condition.
- II. The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM).
- III. The NovoTTF-100A™ System (Novocure Ltd., Haifa, Israel) was approved by the U.S. Food and Drug Administration (FDA) in April 2011 to deliver TTF therapy and is intended as a treatment for adult patients (22 years of age or older) with confirmed glioblastoma multiforme, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment, and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted.
- IV. The NovoTTF-100A System (Novocure Ltd, Haifa, Israel) was approved by the U.S. Food and Drug Administration (FDA) in October 2015 to deliver TTF therapy and is intended as a treatment for adult patients (22 years of age or older) with newly-diagnosed glioblastoma multiforme when given along with the chemotherapy drug temozolomide following standard treatments that include surgery, and radiation therapy and chemotherapy used together.
- V. The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.



<b>SUBJECT: TUMOR–TREATMENT FIELD THERAPY FOR GLIOBLASTOMA</b>	<b>EFFECTIVE DATE: 05/28/15 REVISED DATE: 08/18/16</b>
<b>POLICY NUMBER: 6.01.45 CATEGORY: Technology Assessment</b>	<b>PAGE: 2 OF: 5</b>

### **DESCRIPTION:**

Glioblastoma multiforme (GBM) is the most common and aggressive primary intracranial tumor with approximately 33% surviving 1 year and less than 5% surviving more than 5 years. Median survival with optimal therapy has been reported to be 10-15 months with most tumors recurring within 7-9 months despite multimodal treatment (e.g. repeat surgery, re-irradiation and chemotherapy). Choice of chemotherapy for treatment in the case of recurrence varies but may include alkylating agents (e.g., lomustine, carmustine, procarbazine), re-treatment with temozolomide, and more recently, bevacizumab either alone or in combination with other agents. Overall survival after recurrence is relatively short even with optimal therapy. New or novel treatments such as TTF therapy are being investigated to improve survival in patients with GBM.

TTF therapy is delivered via the NovoTTF-100A™ System which is a battery-powered, portable device that generates alternating low intensity, intermediate electrical fields (100-300 kHz) by four disposable electrode arrays (replaced 1-2 times per week) that are noninvasively attached to the patient's shaved scalp placed in such a way to encompass the tumor. The alternating low intensity electrical field is thought to disrupt cell division of the cancer cells so that either cell division does not occur or it is ineffective, resulting in death of the cancer cells without harming the normal healthy cells. The device is used by the patient at home on a continuous basis (20-24 h/d) for the duration of treatment, which can last for several months. Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living.

### **RATIONALE:**

The Food and Drug Administration approval of the NovoTTF-100A system was based on a phase 3, multinational prospective RCT (Stupp et al, 2012). Two hundred thirty-seven patients with relapsed or progressive glioblastoma multiforme (GBM), despite conventional radiotherapy were randomized in a 1:1 ratio to receive TTF therapy (delivered by the NovoTTF-100A System) only (n=120) or the best standard of care chemotherapy (active control) (n=117). The choice of chemotherapy regimens varied, reflecting local practice at each of the 28 participating clinical centers which were across 7 countries. Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky Performance Status (KPS) score of 80%. More than 80% of participants had failed 2 or more prior chemotherapy regimens, and 20% had failed bevacizumab prior to study enrollment. Ninety-seven percent (116) of 120 participants in the TTF group started treatment and 93 participants (78%) completed 1 cycle (4 weeks) of therapy. Discontinuation of TTF therapy occurred in 27 participants (22%) due to noncompliance or the inability to handle the device. For each TTF treatment month, the median compliance was 86% (range, 41%-98%), which equaled a mean use of 20.6 hours per day. In the active control group, 113 (97%) of the 117 assigned participants received chemotherapy and all except 1 individual completed a full treatment course. Twenty-one participants (18%) in the active control group did not return to the treating site and details on disease progression and toxicity were not available. This RCT did not reach its primary end point of improved survival compared with active chemotherapy. With a median follow-up of 39 months, 220 participants (93%) had died. Median survival was 6.6 months in the TTF group compared with 6.0 months in the active control group (hazard ratio, 0.86; 95% confidence interval [CI], 0.66 to 1.12; p=0.27). For both groups, 1-year survival was 20%. The survival rates for 2- and 3-year survival were 8% and 4%, respectively, for the TTF group versus 5% and 1%, respectively, for the active control group. PFS rate at 6 months was 21.4% in the TTF group, compared with 15.1% in the active control group (p=0.13). Objective radiologic responses (partial and complete response) were noted in 14 participants in the TTF group and 7 in the active control group, with a calculated response rate of 14.0% (95% CI, 7.9% to 22.4%) versus 9.6% (95% CI, 3.9% to 18.8%), respectively. Sixteen percent of the TTF participants had grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids. Active control participants experienced grade 2-4 events by organ system related to the pharmacologic activity of chemotherapy agents used; severe (grades 3 and 4) toxicity was observed in 3% of participants. Longitudinal quality of life (QOL) data were available in 63 participants (27%). There were no meaningful differences observed between the groups in the domains of global health and social functioning. However, cognitive, emotional, and role functioning favored TTF therapy, whereas physical functioning favored chemotherapy. Symptom scale analysis was in accordance to treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the TTF group. In summary, this RCT failed to demonstrate the primary end point of improved survival with TTF therapy in comparison to



<b>SUBJECT: TUMOR–TREATMENT FIELD THERAPY FOR GLIOBLASTOMA</b>  <b>POLICY NUMBER: 6.01.45</b> <b>CATEGORY: Technology Assessment</b>	<b>EFFECTIVE DATE: 05/28/15</b> <b>REVISED DATE: 08/18/16</b>  <b>PAGE: 3 OF: 5</b>
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chemotherapy. Limitations of the trial included a somewhat heterogeneous patient population, with participants included after progression of 1 or several lines of chemotherapy, as well as the use of different chemotherapy regimens in the control group. Another limitation is the absence of a placebo/supportive care arm. In the setting of advanced disease, the supportive care arm would have been useful to gauge the safety and efficacy of treatment for both groups of patients. Treatments used in the active control arm (best standard of care chemotherapy) in the recurrent disease setting have previously demonstrated limited efficacy, thus limiting the ability to determine the true treatment effect of TTF. Data from a trial of TTF versus placebo, or TTF plus standard chemotherapy versus standard chemotherapy alone would therefore provide a better assessment of treatment efficacy.

A subgroup analysis of patient data of this phase 3 trial (Wong et al, 2014) evaluated the different characteristics of responders and nonresponders in the TTF group compared to the active control group. More patients in the TTF arm were considered responders (14/120 vs 7/117 in the chemotherapy arm.) Median response time was longer for those in the TTF arm than the chemotherapy arm (7.3 months vs 5.6 months,  $p < 0.001$ ), and there was a strong correlation (Pearson's  $r$ ) between response and OS in the TTF arm ( $p < 0.001$ ) but not in chemotherapy arm ( $p = 0.29$ ). Compared with the chemotherapy arm, a higher proportion of responders in the TTF arm had a prior low-grade histology (36% vs 0%). These differences in treatment responder groups suggest that TTF therapy may differentially benefit certain types of GBM; however, the small numbers of responders in both groups limits generalizations that can be drawn from this analysis.

Analysis of the NovoTTF-100A™ Patient Registry Dataset (PRiDe) of 457 patients with recurrent GBM who were treated with NovoTTF therapy in the United States between October 2011 and November 2013 and comparison to patient data in the Phase 3 trial was performed (Mrugula et al 2014) to provide a larger dataset of patients with recurrent GBM treated with TTF therapy. No new adverse events in the PRiDe group of patients were reported compared to the Phase 3 trial group. However median overall survival was longer in the TTF group in the PriDe group (9.6 months) compared to the TTF group in the Phase 3 trial (6.6 months) or in the active chemotherapy group (6.0 months). Median treatment time was almost double for the TTF PriDe group compared to either the TTF or chemotherapy group in the Phase 3 trial. Favorable prognostic factors in the PriDe group included 75% or more daily compliance of the device, treatment with TTF at first recurrence, no prior treatment with bevacizumab, and Karnofsky Performance Score (KPS) 90 or greater. The authors suggest there are subsets of patients who derive significant benefit from TTF therapy and that TTF therapy using the NovoTTF-100A™ device is safe and efficacious to treat recurrent GBM.

The Food and Drug Administration approval of the NovoTTF-100A system for newly diagnosed glioblastoma multiforme (GBM) was based on the results from a clinical trial involving 695 patients newly diagnosed with GBM that compared those who used the device with temozolomide (TMZ) to those receiving TMZ alone (Stupp, 2015). Patients who used the device along with TMZ lived, on average, about 7 months with no disease progression compared to 4 months for those who had the drug alone. The device plus TMZ group survived for an average of 19.4 months after starting treatment compared to 16.6 months for those who were treated with TMZ alone.

The use of TTF therapy has been described in a number of case series. However, without evidence from additional high quality comparative studies, these studies provide limited additional evidence about whether TTF therapy improves outcomes compared with currently available therapy for GBM.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Central Nervous System (v 1.2015) states that alternating electrical field therapy for glioblastoma may be considered as a treatment option for recurrent disease (Category 2B).



<b>SUBJECT: TUMOR–TREATMENT FIELD THERAPY FOR GLIOBLASTOMA</b>	<b>EFFECTIVE DATE: 05/28/15 REVISED DATE: 08/18/16</b>
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**CODES:**      Number      Description

*Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).

**CPT:**      There are no specific CPT codes for tumor treatment field therapy.

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**HCPCS:**      A4555      Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only

E0766      Electrical stimulation device used for cancer treatment, includes all accessories, any type

**ICD9:**      191.0-191.9      Malignant neoplasm of brain (code range)

**ICD10:**      C71.0-C71.9      Malignant neoplasm of brain (code range)

**REFERENCES:**

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\* key article



<b>SUBJECT: TUMOR–TREATMENT FIELD THERAPY FOR GLIOBLASTOMA</b>	<b>EFFECTIVE DATE: 05/28/15</b> <b>REVISED DATE: 08/18/16</b>
<b>POLICY NUMBER: 6.01.45</b> <b>CATEGORY: Technology Assessment</b>	<b>PAGE: 5 OF: 5</b>

**KEY WORDS:**

Electric field therapy, NovoTTF-100A, glioblastoma.

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## CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

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There is currently a Local Coverage Determination (LCD) for Tumor Treatment Field Therapy. Please refer to the following LCD website for Medicare Members: [https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34823&ContrId=389&ver=9&ContrVer=1&CtrctrSelected=389\\*1&Ctrctr=389&s=41&DocType=Active&bc=AggAAIAAAAAAAAA%3d%3d&](https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34823&ContrId=389&ver=9&ContrVer=1&CtrctrSelected=389*1&Ctrctr=389&s=41&DocType=Active&bc=AggAAIAAAAAAAAA%3d%3d&).



**Policy: MP306**

**Section: Medical Benefit Policy**

**Subject: Tumor Treatment Fields**

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**I. Policy:** Tumor Treatment Fields

**II. Purpose/Objective:**

To provide a policy of coverage regarding Tumor Treatment Fields

**III. Responsibility:**

- A. Medical Directors
- B. Medical Management

**IV. Required Definitions**

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

**V. Additional Definitions**

Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

- a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
- b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
- c. in accordance with current standards of good medical treatment practiced by the general medical community.
- d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and
- e. the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient.

**Medicaid Business Segment**

Medical Necessity shall mean a service or benefit that is compensable under the Medical Assistance Program and if it meets any one of the following standards:

- (i) The service or benefit will, or is reasonably expected to, prevent the onset of an illness, condition or disability.
- (ii) The service or benefit will, or is reasonably expected to, reduce or ameliorate the physical, mental or development effects of an illness, condition, injury or disability.
- (iii) The service or benefit will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for members of the same age.



**DESCRIPTION:** Tumor Treating Fields, or TTF are low intensity, alternating electric fields within the intermediate frequency range. TTF disrupts cell division through physical interactions with key molecules during mitosis. TTF are generated via pairs of transducer arrays placed directly on the skin's surface in the region surrounding the tumor. The Optune™ delivery system is portable and is designed to allow individuals to continue their daily activities while receiving treatment. This non-invasive treatment is intended as a treatment for adults with histologically-confirmed glioblastoma multiforme (GBM).

**INDICATIONS: REQUIRES PRIOR AUTHORIZATION BY A PLAN MEDICAL DIRECTOR OR DESIGNEE**

**ALL Durable Medical Equipment provided for home use requires advanced determination of coverage. Devices furnished at inpatient or outpatient centers are NOT SEPARATELY REIMBURSABLE.**

The Optune™ tumor treatment field delivery system may be considered medically necessary when **all of the following** criteria are met:

1. As concomitant therapy with temzolomide in newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy; **and**
  - Member is an adult (defined by the FDA for this device as age 22 years or older); **and**
  - Karnofsky Performance Scale\* score of 70 or greater, or Eastern Cooperative Oncology Group (ECOG) performance status\*\* 0-1; **and**
  - Member is capable and agreeable to utilizing the device for a minimum of 18 hours per day

**or**

2. As a monotherapy for recurrent histologically-or radiologically-confirmed glioblastoma multiforme recurrence in the supratentorial region of the brain after receiving chemotherapy;
  - Member is an adult (defined by the FDA for this device as age 22 years or older); **and**
  - Karnofsky Performance Scale\* score of 70 or greater, or Eastern Cooperative Oncology Group (ECOG) performance status\*\* 0-1; **and**
  - Member is capable and agreeable to utilizing the device for a minimum of 18 hours per day

**NOTE:**

\* Karnofsky Performance Status Score:

100	Able to work. Normal; No complaints; No evidence of disease.
90	Able to work. Able to carry on normal activity; Minor symptoms.
80	Able to work. Normal activity with effort; Some symptoms.
70	Independent; not able to work. Cares for self; Unable to carry on normal activity.
60	Disabled; dependent. Requires occasional assistance; cares for most needs.
50	Moderately disabled; dependent. Requires considerable assistance and frequent care.
40	Severely disabled; dependent. Requires special care and assistance.
30	Severely disabled. Hospitalized, death not imminent.
20	Very sick. Active supportive treatment needed.
10	Moribund. Fatal processes are rapidly progressing

**\*\* Eastern Cooperative Oncology Group (ECOG) Performance Status**

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

**LIMITATION:** Authorization for this device will be for a period of one (1) year.



**EXCLUSIONS:**

**For the Medicare business segment**, the use of TTF devices for the treatment of glioblastoma multiforme or any other indication is considered not reasonable and necessary, and therefore **NOT COVERED** per L34823 Tumor Treatment Field Therapy.

**For the Medicaid business segment**, the use of TTF devices for cancer treatment is considered experimental/investigational and **NOT COVERED** per MCOPS Memo #06/2016-006

The use of TTF devices to treat other malignant tumors (including but not limited to breast, lung, pancreatic, solid tumor brain metastases, ovarian and melanoma) and all other indications is considered Experimental, Investigational or Unproven and therefore, **NOT COVERED**.

**Note: A complete description of the process by which a given technology or service is evaluated and determined to be experimental, investigational or unproven is outlined in MP 15 - Experimental Investigational or Unproven Services or Treatment.**

**CODING ASSOCIATED WITH: Tumor Treatment Fields**

*The following codes are included below for informational purposes and may not be all inclusive. Inclusion of a procedure or device code(s) does not constitute or imply coverage nor does it imply or guarantee provider reimbursement. Coverage is determined by the member specific benefit plan document and any applicable laws regarding coverage of specific services. Please note that per Medicare coverage rules, only specific CPT/HCPCS Codes may be covered for the Medicare Business Segment. Please consult the CMS website at [www.cms.gov](http://www.cms.gov) or the local Medicare Administrative Carrier (MAC) for more information on Medicare coverage and coding requirements.*

77299 Unlisted procedure, therapeutic radiology clinical treatment planning [when specified as plan for using an electrical stimulation device for TTF]

A4555 Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only

E0766 Electrical stimulation device used for cancer treatment, includes all accessories, any type

J8700 Temozolomide, oral, 5 mg

J9328 Injection, temozolomide, 1 mg

Current Procedural Terminology (CPT®) © American Medical Association: Chicago, IL

**LINE OF BUSINESS:**

**Eligibility and contract specific benefits, limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD's and NCD's will supersede this policy. For PA Medicaid Business segment, this policy applies as written.**

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This policy will be revised as necessary and reviewed no less than annually.

**Devised:** 5/16

**Revised:** 7/16 (updated line of business specific coverage)

**Reviewed:** 5/17



**Effective Date: October 1, 2016**

**Subject: Tumor Treating Fields**

**Overview:** Tumor treating fields (TTF) therapy uses alternating electric fields to inhibit cell proliferation and leads to programmed cell death in the treatment of glioblastoma.

**Policy and Coverage Criteria:**

Harvard Pilgrim considers electric tumor treating fields (TTF) **medically necessary** for the treatment of histologically-confirmed glioblastoma (GBM) in members 18 years of age or older.

Harvard Pilgrim considers TTF **medically necessary** when used with temozolomide (TMZ) for the treatment of adult patients with newly diagnosed, supra-tentorial GBM following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

Harvard Pilgrim considers TTF **medically necessary** for the treatment of recurrent GBM when used as a monotherapy after surgical and radiation options have been exhausted.

**Exclusions:** Harvard Pilgrim considers TTF **investigational and/or not medically necessary** for the treatment of any condition not outlined above.

**Supporting Information:**

1. Technology Assessment

Tumor treating fields uses the Optune system which consists of 4 sets of insulated electrodes and an electric generator. The electrodes are attached to the shaved scalp of the patient who wears the device for at least 18 hours out of the day while low-intensity alternating electric fields are delivered to the tumor area. The alternating electric fields inhibit cell proliferation and lead to programmed cell death. The therapy targets dividing cells to stop tumor growth while sparing normal tissue.

2. Literature Review

Emerging evidence supports the use TTF to treat glioblastoma in adult patients.

Stupp et al (2015) conducted a phase 3 randomized trial to evaluate the efficacy and safety of TTF used in combination with TMZ maintenance treatment after chemoradiation therapy for patients with glioblastoma. The study enrolled 695 patients. The analysis included 210 patients randomized to TTF plus TMZ and 105 randomized to TMZ alone. Analysis was conducted at a median follow-up of 38 months. Median progression-free survival was 7.1 months in the TTF plus TMZ group and 4.0 months in the TMZ alone group. Median overall survival was 20.5 months in the TTF plus TMZ group and 15.6 months in the TMZ alone group. The trial was terminated based on the results of the interim analysis. The authors concluded that, based on the interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTF to maintenance TMZ chemotherapy significantly prolonged progression-free and overall survival.

Mahadevan et al (2015) conducted a retrospective review of 40 patients with malignant gliomas who were treated with TTF or TTF with stereotactic radiosurgery (SRS). All patients had failed TMZ chemo-irradiation. Of the 40 patients, 12 received TTF and SRS. The median overall survival from initiation of TTF was 8 months. Those who were treated with TTF and SRS showed an increase in median overall survival compared with the TTF only group, 4 versus 12 months. The authors concluded there may be a benefit to combining TTF and SRS therapies to treat patients with recurrent glioblastoma.



Vymazal and Wong (2014) analyzed the results from two prior studies with demonstrated radiologic tumor response to single-agent TTF in patients with recurrent glioblastoma. The aim of the analysis was to better characterize tumor response patterns and evaluate associations between response, compliance, and overall survival. The overall response rate across both trials was 15%. Response duration was correlated with overall survival, and median overall survival for responders was 24.8 months. Compliance was linked with both improved response and survival. Seven of 16 responders exhibited tumor growth before shrinkage.

Stupp et al (2012) conducted a phase III trial of chemotherapy-free treatment of TTF (20-24 h/day) versus active chemotherapy in the treatment of patients with recurrent glioblastoma. A total of 120 patients received TTF alone and 117 patients received chemotherapy alone. Median survival was 6.6 months in the TTF group versus 6.0 months in the chemotherapy group, which held no significant difference. There was no difference in 1-year survival rate or progression-free survival rate at 6 months. There were significantly less severe adverse events in the TTF group (6%) versus the chemotherapy group (16%) and the quality of life analyses favored TTF therapy in most domains. The authors concluded that no improvement in overall survival was demonstrated, however efficacy and activity with TTF appears comparable to chemotherapy regimens that are commonly used for glioblastoma. Toxicity and quality of life clearly favored TTF.

**Pless and Weinberg (2011) published an expert opinion stating "[t]he proof of concept of TTFields has been well demonstrated in the preclinical setting, and the clinical data seem promising in various tumor types. The side effects of TTFields were minimal and in general consisted of skin reaction to the electrodes. There are a number of ways in which TTFields could be further evaluated, for example, in combination with chemotherapy, as a maintenance treatment, or as a salvage therapy if radiotherapy or surgery is not possible."**

Salzberg et al (2008) conducted an open, prospective pilot study to evaluate the safety, tolerability, and efficacy profile of TTF treatment in patients with locally advanced and/or metastatic solid tumors using the NovoTTF100A device. The cohort included 6 patients who were heavily pre-treated with several lines of therapy. Patients received TTF treatment for a minimum of 14 days. No serious adverse events occurred. Outcomes showed a partial response of a skin metastasis from primary breast cancer, 3 cases where tumor growth was arrested during treatment, and 1 case of disease progression. The authors concluded that while the cohort was small, the lack of therapy toxicity and the efficacy observed in data gathered indicates the potential of TTF as a treatment modality for solid tumors.

### 3. Professional/Governmental Organizations

FDA: Optune is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune with temozolomide (TMZ) is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

For the treatment of recurrent GBM, Optune is indicated following histologically- or radiologically-confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

[http://www.accessdata.fda.gov/cdrh\\_docs/pdf10/P100034S013b.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034S013b.pdf)

NCCN: Approval of TTF by the FDA in 2011 for the treatment of recurrent glioblastoma was based on a clinical trial that randomized 237 patients to TTF or chemotherapy. Similar survival was seen in the two arms, and TTF therapy was associated with lower toxicity and improved quality of life. Due to lack of efficacy, not all panelists recommend the treatment.

[http://www.nccn.org/professionals/physician\\_gls/pdf/cns.pdf](http://www.nccn.org/professionals/physician_gls/pdf/cns.pdf)

### Codes:

HCPCS code:

E0766 – Electrical stimulation device used for cancer treatment, includes all accessories, any type

Medically necessary ICD-9 codes:



191.0 – malignant neoplasm of brain – Cerebrum, except lobes and ventricles (i.e. basal ganglia, cerebral cortex, corpus striatum, globus pallidus, hypothalamus, thalamus)  
 191.1 – malignant neoplasm of the brain – frontal lobe  
 191.2 – malignant neoplasm of the brain – temporal lobe (i.e. hippocampus, uncus)  
 191.3 – malignant neoplasm of the brain – parietal lobe  
 191.4 – malignant neoplasm of the brain – occipital lobe  
 191.5 – malignant neoplasm of the brain – ventricles (i.e. choroid plexus, floor of ventricles)  
 191.6 – Cerebellum NOS (i.e. cerebellopontine angle)  
 191.7 – malignant neoplasm of the brain – brain stem (i.e. cerebral peduncle, medulla oblongata, midbrain, pons)  
 191.8 – malignant neoplasm of the brain – other parts of the brain (i.e. corpus callosum, tapetum)  
 191.9 – malignant neoplasm of the brain – brain, unspecified (i.e. cranial fossa NOS)

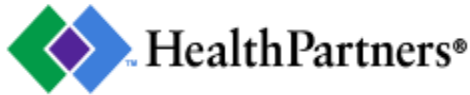
Medically necessary ICD-10 codes:

C71.0 – malignant neoplasm of cerebrum, except lobes and ventricles (i.e. malignant neoplasm of supratentorial NOS)  
 C71.1 – malignant neoplasm of frontal lobe  
 C71.2 – malignant neoplasm of temporal lobe  
 C71.3 – malignant neoplasm of parietal lobe  
 C71.4 – malignant neoplasm of occipital lobe  
 C71.5 – malignant neoplasm of cerebral ventricle  
 C71.6 – malignant neoplasm of cerebellum  
 C71.7 – malignant neoplasm of brain stem (i.e. malignant neoplasm of 4<sup>th</sup> cerebral ventricle, infratentorial malignant neoplasm NOS)  
 C71.8 – malignant neoplasm of overlapping sites of brain  
 C71.9 – malignant neoplasm of brain, unspecified

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## Electric tumor treatment fields (ETTF) to treat glioblastoma (Optune)™

[Print](#)

These services may or may not be covered by your HealthPartners plan. Please see your plan documents for your specific coverage information. If there is a difference between this general information and your plan documents, your plan documents will be used to determine your coverage.

### Administrative Process

Prior authorization is not required for electric tumor treatment fields to treat glioblastoma.

### Coverage

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Electric tumor treatment fields (ETTF) therapy is generally covered subject to the indications listed below and per your plan documents.

### Indications that are covered

Electric tumor treatment fields (ETTF) therapy is covered as follows:

1. For patients with glioblastoma (GBM) that recurs or progresses after initial treatment; or



2. As a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM) in combination with temozolomide; or
3. For the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery, and completion of radiation therapy together with concomitant standard of care chemotherapy; or
4. For the treatment of recurrent GBM following histologically-or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

## Indications that are not covered

Electric tumor treatment fields (ETTF) is not covered for any additional indications.

## Definitions

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Tumor treating fields (TTFs) therapy uses alternating electric fields to inhibit cell proliferation and lead to programmed cell death. TTF therapy targets dividing cells to stop tumor growth while sparing normal tissue. The Optune™ TTF system is intended to treat patients with glioblastoma by using transducer arrays placed on the patient's scalp according to the tumor's location. Patients use the device on an outpatient basis for at least 18 hours per day for 4 weeks to several months. Intended benefits include stabilizing the disease, having fewer treatment-related adverse events, and improving quality of life.

## Codes

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*If available, codes for a procedure, device or diagnosis are listed below for informational purposes only, and do not guarantee member coverage or provider reimbursement. The list may not be all inclusive.*

Codes	Description
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type
A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only

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## Products

This information is for most, but not all, HealthPartners plans. Please read your plan documents to see if your plan has limits or will not cover some items. If there is a difference between this general information and your plan documents, your plan documents will be used to determine your coverage. These coverage criteria may not apply to Medicare Products if Medicare requires different coverage. For more information regarding Medicare coverage criteria or for a copy of a Medicare coverage policy, contact Member Services at **952-883-7979** or **1-800-233-9645**.

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## Policy activity

- 08/21/2013 - Date of origin
- 08/21/2013 - Effective date

## Review date

- 07/2015

## Revision date

- 04/12/2016

## Related content



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# Highmark Commercial Medical Policy - Pennsylvania

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<b>Medical Policy:</b>	E-5-005
<b>Topic:</b>	Tumor Treatment Fields (TTF)
<b>Section:</b>	Durable Medical Equipment
<b>Effective Date:</b>	March 20, 2017
<b>Issue Date:</b>	June 4, 2018
<b>Last Reviewed:</b>	May 2018

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Electrical fields, known as "tumor treatment fields" (TTF), are created by low-intensity, alternating intermediate frequency (100-200 kilohertz [kHz]) electric currents delivered to the malignant tumor site by insulated electrodes placed on skin surface of the tumor site. As a result of the unique shape and electrical characteristics of dividing tumor cells, TTF exposure may damage the dividing cells through anti-microtubule mechanisms and could stop tumor growth while sparing normal tissue.

*This policy is designed to address medical guidelines that are appropriate for the majority of individuals with a particular disease, illness, or condition. Each person's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.*

**Policy Position** Coverage is subject to the specific terms of the member's benefit plan.

TTF may be considered medically necessary when **ALL** of the following indications are met:

- When it is used as an alternative to standard medical therapy, as a monotherapy; **and**
- For treatment of adult patients (22 years of age or older); **and**
- With histologically-confirmed glioblastoma multiforme; **and**
- Following histologically- or radiologically-confirmed recurrence in the Supratentorial region of the brain; **and**
- After receiving chemotherapy; **and**
- After surgical and radiation options have been exhausted.

**OR**

TTF may be considered medically necessary when **ALL** of the following indications are met:

- It is used as an adjunct to standard maintenance therapy; **and**
- For treatment for adult patients (22 years of age or older); **and**
- With histologically-confirmed glioblastoma multiforme; **and**
- When it is used with temozolomide; **and**
- With newly diagnosed, supratentorial glioblastoma, **and**
- Following maximal debulking surgery; **and**
- Completion of radiation therapy; **and**



- Together with concomitant standard of care chemotherapy.

TTF is considered experimental/investigational when above criteria are not met or for any other indications, and therefore, not covered because the safety and/or effectiveness of this service cannot be established by the available published peer-reviewed literature.

#### **Procedure Codes**

A4555, E0766

### **Place of Service: Inpatient/Outpatient**

Experimental/Investigational (E/I) services are not covered regardless of place of service.

The use of tumor treatment fields is typically an outpatient procedure which is only eligible for coverage as an inpatient procedure in special circumstances, including, but not limited to, the presence of a co-morbid condition that would require monitoring in a more controlled environment such as the inpatient setting.


### **The policy position applies to all commercial lines of business**

### **Denial Statements**

Services that do not meet the criteria of this policy will be considered experimental/investigational (E/I). A network provider can bill the member for the experimental/investigational service. The provider must give advance written notice informing the member that the service has been deemed E/I. The member must be provided with an estimate of the cost and the member must agree in writing to assume financial responsibility in advance of receiving the service. The signed agreement must be maintained in the provider's records.

### **Links**

- [Link to Diagnosis Codes](#)
- [Link to References](#)

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Room 509F, HHH Building  
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**Horizon BCBSNJ**

Uniform Medical Policy Manual Section: D M E  
 Policy Number: 042  
 Effective Date: 07/10/2018  
 Original Policy Date: 09/24/2013  
 Last Review Date: 07/10/2018  
 Date Published to Web: 09/24/2013

**Subject:**

Tumor-Treatment Fields Therapy

**Description:****IMPORTANT NOTE:**

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Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

Populations	Interventions	Comparators	Outcomes
Individuals: · With newly diagnosed glioblastoma multiforme on maintenance therapy after initial treatment	Interventions of interest are: · Tumor treating fields therapy as an adjunct to standard maintenance therapy	Comparators of interest are: · Standard maintenance therapy alone	Relevant outcomes include: · Overall survival · Disease-specific survival · Quality of life · Treatment-related morbidity
Individuals: · With progressive or recurrent glioblastoma multiforme	Interventions of interest are: · Tumor treating fields therapy as an adjunct or alternative to medical therapy	Comparators of interest are: · Standard medical therapy	Relevant outcomes include: · Overall survival · Disease-specific survival · Quality of life · Treatment-related morbidity

**Background****Glioblastoma Multiforme**

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.<sup>1</sup> GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (eg, bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors.<sup>1</sup> The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to 1 year, and the 5-year survival rate was around 5%.<sup>2</sup>

**Clinical Context and Therapy Purpose**

The purpose of alternating electrical field therapy, more commonly known as tumor treating fields (TTF) therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

**Treatment of Newly Diagnosed GBM**

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these 2 therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles.

Response and overall survival rates with temozolomide are higher in patients who have O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation (see 'Analysis of MGMT Promoter Methylation in Malignant Gliomas' - Policy #098 in the Pathology Section).

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice (see the Supplemental Information section).<sup>3</sup> For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially all patients.

**Treatment of Recurrent GBM**

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivasculature endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (eg, lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%.<sup>4</sup> There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.



- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

### Patients

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

### Interventions

TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields.<sup>4-6</sup> TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. TTF therapy is proposed to inhibit tumor growth by 2 mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase.<sup>5,6</sup> Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune (formerly NovoTTF-100A System) is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

### Comparators

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

The following practices are currently being used to make decisions about recurrent GBM: medical therapy.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months.<sup>4</sup>

### Outcomes

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

### Timing

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

### Setting

The setting is outpatient care by an oncologist or neuro-oncologist.

### Regulatory Status

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.<sup>7</sup> The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (18 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved Novocure's request for a product name change from NovoTTF-110A System to Optune®.<sup>8</sup>

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.<sup>9</sup> The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

FDA product code: NZK.

### Related Policies

- Analysis of MGMT Promoter Methylation in Malignant Gliomas (Policy #098 in the Pathology Section)
- Radiation Therapy for Primary Craniospinal Tumors and Neurologic Conditions (Policy #100 in the Radiology Section)
- Intracavitary Balloon Catheter Brain Brachytherapy for Malignant Gliomas or Metastasis to the Brain (Policy #077 in the Radiology Section)

### Policy:

(NOTE: For Medicare Advantage, please refer to the Medicare Coverage Section below for coverage guidance.)

1. Tumor treating fields therapy to treat glioblastoma multiforme is considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in members with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

- Adult patients ≥18 years of age
- Supratentorial tumor
- Karnofsky Performance Status score ≥70%
- Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (see Policy Guidelines).

2. Tumor treating fields therapy is considered **investigational** in all other conditions including but not limited to the following situations:

- As an adjunct to standard medical therapy (e.g., bevacizumab, chemotherapy) for members with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for members with progressive or recurrent glioblastoma multiforme
- For brain metastases
- For cancer in areas other than the brain.



**Medicare Coverage:**

There is no National Coverage Determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of Local Medicare Carriers. Nori Healthcare Services, LLC, the Local DME Medicare Carrier for jurisdiction JA, has issued determination L34823 Tumor treatment field therapy. Per LCD L348 Tumor treatment field therapy, (E0766) will be denied as not reasonable and necessary. Per Local Policy Article A52711, HCPCS code A4555 is not valid for billing to Medicare and will be denied an invalid code.

For additional information, refer to Local Coverage Determination (LCD): Tumor Treatment Field Therapy (TTFT) (L34823). Available at: [https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34823&ContrlId=389&ver=14&ContrVer=1&CntrctrSelected=389\\*1&Cntrctr=389&s=38&DocType=All&bc=AggAAAQAAAAAA%3d%3d&](https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34823&ContrlId=389&ver=14&ContrVer=1&CntrctrSelected=389*1&Cntrctr=389&s=38&DocType=All&bc=AggAAAQAAAAAA%3d%3d&)

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Local Coverage Article: Tumor Treatment Field Therapy (TTFT) - Policy Article (A52711). Available at: [https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=52711&ver=10&LCDId=34823&ContrlId=389&ContrVer=1&CntrctrSelected=389\\*1&Cntrctr=389&s=38&DocType=All&bc=AggAAAQAAAAAA%3d%3d&](https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=52711&ver=10&LCDId=34823&ContrlId=389&ContrVer=1&CntrctrSelected=389*1&Cntrctr=389&s=38&DocType=All&bc=AggAAAQAAAAAA%3d%3d&)

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**Policy Guidelines:** (Information to guide medical necessity determination based on the criteria contained within the policy statements above.)

Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth >25% compared with the smallest tumor area measured in the patient during the trial or appearance of 1 or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme) The Food and Drug Administration label includes the following notices:

- Patients should use Optune for at least 18 hours a day to get the best response to treatment
- Patients should finish at least 4 full weeks of therapy to get the best response to treatment. Stopping treatment before 4 weeks lowers the chances of a response to treatment.

**RATIONALE:** This policy was created in 2013 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through April 5, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

For this review, 3 indications are evaluated: (1) tumor treating fields (TTF) as an adjunct to maintenance chemotherapy in newly diagnosed patients following initial treatment with surgery, radiotherapy and chemotherapy and (2) TTF as an adjunct or (3) alternative to medical therapy (eg, bevacizumab, chemotherapy, progressive or recurrent glioblastoma multiforme (GBM)).

**Study Selection**

The PICOTS was used to select relevant studies.

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Within each category of study design, studies with larger sample size studies and longer duration were sought.

**TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM****Randomized Controlled Trials**

Stupp et al (2017) published results of the EF-14 multicenter, open-label phase 3 RCT that evaluated maintenance therapy with TTF for newly diagnosed GBM. The trial included 695 patients from 83 sites who had supratentorial GBM and had completed standard treatment consisting of biopsy or surgical resection followed by radiotherapy and chemotherapy (see Table 1). A Karnofsky Performance Status (KPS) score of 70 or higher was an additional inclusion criterion to ensure independence in activities of daily living, and patients with rapidly progressing GBM following radiochemotherapy were excluded from the trial. Patients were randomized in a 2:1 fashion to TTF plus maintenance temozolomide or maintenance temozolomide alone.

All patients were seen monthly for follow-up. Quality of life (QOL) was assessed every 3 months, and magnetic resonance imaging (MRI) was performed every 6 months until tumor progression. Tumor progression on MRI was adjudicated by a central review committee blinded to treatment group. The primary outcome was progression-free survival (PFS), and the secondary outcome was overall survival (OS). The analysis was by intention-to-treat, including 26 patients from the control arm who crossed over to TTF following the planned interim analysis.

In 2014, an independent data and safety monitoring board concluded from the planned interim analysis that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended trial termination. The Food and Drug Administration approved the trial termination, and the trial was closed to recruitment with 695 of the planned 700 participants randomized. Control arm participants were allowed to cross over to the experimental treatment at this time. The interim analysis, which the Food and Drug Administration considered for the 2015 expanded approval of Optune, was published by Stupp et al (2015).<sup>11</sup> At the time of the interim analysis, data were available for 210 patients randomized to TTF plus temozolomide and 105 patients to temozolomide alone. Follow-up of the remainder of the 695 enrolled patients continued after enrollment was closed.

**Table 1. Key Randomized Controlled Trial Characteristics for Newly Diagnosed Glioblastoma**

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Stupp et al (2017) <sup>10</sup> ; EF-14	U.S., E.U., South Korea, Israel	83	2009-2016	<ul style="list-style-type: none"> <li>· 695 newly diagnosed with GBM and treated by radiochemotherapy</li> <li>· KPS score ≥70</li> </ul>	TTF >18 h/d plus maintenance temozolomide (n=466)	Maintenance temozolomide alone (5 d every 28 d for 6 cycles) (n=229)

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GBM: glioblastoma multiforme; h/d: hours per day; KPS: Karnofsky Performance Status; TTF: tumor treatment fields.



Results of the final analysis of the EF-14 trial were similar to the interim analysis and are shown in Table 2. Both PFS and OS improved with the addition of TTF therapy to standard maintenance chemotherapy (ie, temozolomide). PFS increased by 2.7 mo ( $p<0.001$ ) and OS increased by 4.9 mo ( $p<0.001$ ) in the TTF group. The time to a decrease in mental function was 2.5 months longer with TTF therapy ( $p<0.01$ ).

There was a similar percentage of dropouts at the final analysis with 49 (11%) patients in the TTF group and 27 (12%) patients in the temozolomide alone group. More treatment cycles with temozolomide were administered in the TTF group (median, 6 for TTF group vs 5 for controls), a finding that is consistent with the longer PFS. Rates of adverse events were similar between the groups, including rates of seizures. In secondary analysis of patients who had not progressed, there was no reduction in health-related quality of life with TTF compared with temozolomide alone aside from "itchy skin".<sup>12</sup> Interpretation of this result is limited by the low percentage of patients who completed the health-related quality of life assessments at follow-up (65.8% of the 655 patients alive at 3 months and 41.7% of the 473 patients alive at 12 months). A mixed-model analysis, which accounts for missing data, confirmed the results of the mean change from base analysis.

**Table 2. Key Randomized Controlled Trial Results for Newly Diagnosed Glioblastoma**

Study	Final N (%)	Median PFS (95% CI), mo	Median OS (95% CI), mo	Systemic Adverse Events, n (%)	Seizures, n (%)	Time to 6-Point Decline in MMSE Score (95% CI), mo
Stupp et al (2017) <sup>10</sup>						
TTF + temozolomide	417 (89)	6.7 (6.1 to 8.1)	20.9 (19.3 to 22.7)	218 (48)	26 (6)	16.7 (14.7 to 19.0)
Temozolomide alone	202 (88)	4.0 (3.8 to 4.4)	16.0 (14.0 to 18.4)	94 (44)	13 (6)	14.2 (12.7 to 17.0)
HR (95% CI)		0.63 (0.52 to 0.76)	0.63 (0.53 to 0.76)			0.79 (0.66 to 0.95)
P value		<0.001	<0.001	0.58		0.01

CI: confidence interval; HR: hazard ratio; MMSE: Mini-Mental State Examination; OS: overall survival; PFS: progression-free survival; TTF: tumor treatment fields.

Tables 3 and 4 display notable gaps identified in this trial, the major limitation is the lack of patient blinding to treatment assignment. However, PFS was assessed by investigators who were blinded to treatment and placebo effects on OS were expected to be minimal. Investigators considered it practically unfeasible (due to the heat and current of the TTF therapy) and ethically unacceptable to submit the control patients to repeated shaving of the head and continuous wear of a sham device over many months.

**Table 3. Relevance Gaps**

Study; Trial	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Stupp et al (2017) <sup>10</sup> ; EF-14			3. Possible differences in post-progression treatment affecting overall survival		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 4. Study Design and Conduct Gaps**

Study; Trial	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
Stupp et al (2017) <sup>10</sup> ; EF-14		1. No sham control and not blinded to treatment assignment				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence interval and/or p values not reported; 4. Comparative treatment effects not calculated.

## Section Summary: TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM

The final analysis of the EF-14 trial, which included 695 patients from 83 sites, found a statistically and clinically significant increase of 2.7 months in PFS and increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. There was no sham control, and patients were not blinded to treatment assignment, but PFS was assessed by blinded evaluators, and placebo effects on the objective measure of OS were likely to be minimal. There was no evidence of a negative impact of TTF therapy on health-related quality of life, except for itchy skin from the transducers.

## TTF Therapy as an Adjunct or Alternative to Medical Therapy for Progressive or Recurrent GBM

### Randomized Controlled Trials

The 2011 Food and Drug Administration approval of the NovoTTF-100A System (now called Optune) was based on a phase 3 multinational RCT (EF-11), results of which were published by Stupp et al (2012).<sup>4</sup> This trial compared TTF therapy alone with physician's choice medical therapy in 237 adults who had relapsed progressive glioblastoma (see Table 5). Patients had failed conventional treatment with radiotherapy, chemotherapy, and/or surgery, and more than 80% of participants had failed 2 or more prior chemotherapy regimens. In this trial, the term chemotherapy also applied to targeted agents such as bevacizumab. Patient characteristics and performance of additional post-recurrence debulking surgery were similar in the 2 groups.

**Table 5. Summary of Key Randomized Controlled Trial Characteristics for Progressive or Recurrent Glioblastoma**

Study; Trial	Countries	Sites	Dates	Participants	Interventions
Stupp et al (2012) <sup>4</sup> ; EF-11	U.S., E.U., Israel	28	1987-2013	237 adults with relapsed or progressive supratentorial	120 patients treated with TTF alone, 93 (78%) completed 1
					117 patients treated with physician's choice of medical



11				glioblastoma · KPS score $\geq 70\%$	cycle	therapy <sup>a</sup>
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EU: European Union; KPS: Karnofsky Performance Status; TTF: tumor treating fields.

<sup>a</sup> Medical therapy included bevacizumab, irinotecan, nitrosoureas, platinum-based chemotherapy (ie, carboplatin); temozolomide; or a combination of procarbazine, chloroethyl ether, and vincristine.

Participants were followed monthly, including laboratory tests. MRI images were evaluated at 2, 4, and 6 months from initiation of treatment, with subsequent MRIs performed according to local practice until disease progression. QOL questionnaires were completed every 3 months. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess mortality rates. The primary end point was overall survival. Secondary end points included PFS, the percentage of patients with PFS at 6 months, time to progression, 1-year survival rate, QOL, and radiologic response rate. End points were evaluated using intention-to-treat analysis.

The trial did not reach its primary end point of improved survival compared with active medical therapy (see Table 6). With a median follow-up of 39 months, 9% of patients had died. There was not a statistically significant difference in survival rates at 1, 2, and 3 years between groups. Patients in the TTF group did not, however, suffer the typical systemic side effects of chemotherapy. The most common adverse event in the TTF group was grade 1 and 2 contact dermatitis of the scalp, which resolved with topical corticosteroids and did not require treatment breaks. Control participants experienced grade 2, 3, or 4 events by organ system related to the pharmacologic activity of chemotherapy agents used. Hematologic events of grade 2 or greater were observed in 17% of chemotherapy patients compared with 3% of TTF patients. Gastrointestinal disorders of grade 2 or greater were identified in 17% of chemotherapy patients compared with 4% of TTF patients. Severe (grades 3-4) hematologic and gastrointestinal toxicity was observed in 7% of chemotherapy controls compared with 1% of the TTF group.

Longitudinal QOL data, available in 63 (27%) participants, showed no meaningful differences between groups for the domains of global health and social functioning. However, cognitive and emotional functioning domains favored TTF therapy. Symptom scale analysis was by treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.

The trial had a number of limitations (see Tables 7 and 8), that included lack of blinding and high loss to follow-up. Discontinuation of TTF therapy occurred in 22% of patients due to noncompliance or inability to handle the device, usually within the first few days. In the control group, 21 (18%) patients did not return to the treatment site, and details on disease progression and toxicity were not available. Longitudinal QOL could be analyzed only for 27% of patients who remained on study therapy for 3 months. The trial was designed as a superiority trial and did not provide adequate evidence of noninferiority.

**Table 6. Summary of Key Randomized Controlled Trial Results for Recurrent or Progressive Glioblastoma**

Study; Trial	LTFU, n (%)	Median OS, mo	Progression-Free Survival		Overall Survival (95% CI), %		
			Median, mo	Rate at 6 Months (95% CI), %	1 Year	2 Years	3 Years
Stupp et al (2012) <sup>4</sup> ; EF-11							
TTF	23 (22)	6.6	2.2	21.4 (13.5 to 29.3)	20	8 (4 to 13)	4 (1 to 8)
PCC	12 (18)	6.0	2.1	15.1 (7.8 to 22.3)	20	5 (3 to 10)	1 (0 to 3)
HR (95% CI)		0.86 (0.66 to 1.12)	0.81 (0.60 to 1.09)				
P value		0.27	0.16	0.13			

CI: confidence interval; HR: hazard ratio; LTFU: loss to follow-up; PCC: physician's choice chemotherapy; TTF: tumor treating fields.

**Table 7. Relevance Gaps**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Stupp et al (2012) <sup>4</sup> ; EF-11			2. Physician's choice chemotherapy		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not established and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 8. Study Design and Conduct Gaps**

Study; Trial	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>d</sup>	Data Completeness <sup>e</sup>	Power <sup>d</sup>	Statistical <sup>f</sup>
Stupp et al (2012) <sup>4</sup> ; EF-11		1. Not blinded to treatment assignment		1. 78% of TTF group completed only 1 cycle of therapy, 18% of control group lost to follow-up 1. Longitudinal QOL data were available for 27% of patients		1. Not designed as a noninferiority trial

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

QOL: quality of life.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence interval and/or p values not reported; 4. Comparative treatment effects not calculated.

#### Nonrandomized Comparative Studies

Kesari et al (2012) conducted a post hoc analysis of the EF-11 trial (see Stupp et al [2012] above) to evaluate the efficacy of TTF in patients who had the first recurrence.<sup>13</sup> Some patients in the temozolomide alone group crossed over to receive TTF plus chemotherapy after the first recurrence, resulting in 144 patients who received TTF fields plus chemotherapy and 60 patients who received chemotherapy alone for recurrent GBM (see Table 9). Patient characteristics and



second-line treatments were well-balanced between the groups, with bevacizumab the most common second-line therapy. The median OS in patients treated with systemic therapy alone was 9.2 months (see Table 10). In comparison, the group of patients who received TTF therapy in addition to systemic therapy had a median OS of 11.8 months ( $p=0.043$ ).

A registry study published Mrugala et al (2014) assessed OS data from patients who received NovoTTF therapy in a real-world, clinical practice setting (see Table 9).<sup>14</sup> Concurrent treatment was not captured in the registry, and it is possible that some patients received combination therapy. Median OS in the PRiDe clinical practice dataset (9.6 mo) was reported as superior to that attained in the EF-11 pivotal trial (6.6 mo,  $p<0.001$ ) (see Table 10). More patients in the PRiDe registry were treated for first recurrence (33% vs 9%), and more had received bevacizumab as prior therapy (55% vs 19%). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

**Table 9. Characteristics of Key Nonrandomized Trial Results**

Study	Study Type	Country	Dates	Participants	TTF	Controls	FU
Kesari et al (2017) <sup>13</sup>	EF-14 post hoc analysis	U.S., E.U., South Korea, Israel	2009-2016	204 patients with first recurrence in the EF-14 trial	144 patients treated with TTF plus second-line chemotherapy	60 patients treated with second-line chemotherapy	12.6 mo
Mrugala et al (2014) <sup>14</sup>	Registry	U.S. (91 centers)	2011-2013	457 patients with recurrent GBM	Patient Registry Dataset (PRiDe)	EF-11	

FU: follow-up; GBM: glioblastoma; TTF: tumor treating fields.

**Table 10. Summary of Key Nonrandomized Trial Results**

Study	Median OS, mo	Median OS With Bevacizumab, mo	
Kesari et al (2017) <sup>13</sup> , EF-14			
TTF plus chemotherapy	11.8	11.8	
Chemotherapy alone	9.2	9.0	
Hazard ratio (95% CI)	0.70 (0.48 to 1.00)	0.61 (0.37 to 0.99)	
P value	0.049	0.043	
		<b>1-Year OS, %</b>	<b>2-Year OS, %</b>
Mrugala et al (2014) <sup>14</sup>			
PRiDe Registry	9.6	44	30
EF-11	6.6	20	9
Hazard ratio (95% CI)	0.66 (0.05 to 0.86)		
P value	<0.001		

CI: confidence interval; OS: overall survival; TTF: tumor treating fields.

Post hoc analyses of the EF-11 pivotal trial have been reported. Wong et al (2014) published a subgroup analysis to determine characteristics of responders & nonresponders in the active treatment and active treatment control.<sup>15</sup> They found that responders had a lower grade of histology and lower daily dexamethasone use than nonresponders. A second post hoc analysis by Kanner et al (2014) of the EF-11 pivotal trial data was performed to evaluate OS among patients who finished at least 1 complete course of TTF or chemotherapy.<sup>16</sup> The investigators reported that median OS was 7.7 months in the TTF group compared with 5.0 months in the chemotherapy group ( $p=0.009$ ). These post hoc analyses are considered to be hypothesis-generating.

#### Section Summary: TTF Therapy as an Adjunct or Alternative to Chemotherapy for Progressive or Recurrent GBM

The single RCT for TTF as an alternative to chemotherapy reported that outcomes following TTF therapy were similar to outcomes following standard chemotherapy. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. The noninferiority of TTF compared with chemotherapy might be considered a sufficient health benefit, if TTF reduced treatment toxicity. However, because the trial was not designed as a noninferiority trial no inferences of noninferiority compared with chemotherapy can be made. Physician's choice therapy during the trial was heterogeneous, although analysis indicates that survival was not affected by choice of chemotherapy. More patients in the TTF group than in the control group did not complete the treatment course. The number of patients who contributed QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators might have been subject to bias due to the lack of blinding.

A nonrandomized post hoc evaluation of the EF-14 trial suggests that TTF may improve survival when combined with chemotherapy for recurrent GBM. This analysis should be considered hypothesis-generating, and further study in high-quality RCTs is needed.

#### Summary of Evidence

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes an RCT. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, & treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

#### Supplemental Information

**Clinical Input From Physician Specialty Societies and Academic Medical Centers** 2112

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic



medical centers, unless otherwise noted.

In response to requests, input was received from 3 physician specialty societies (one of which provided 6 responses and 2 of which provided 1 response each and 1 academic medical center (total of 9 individual responses) while this policy was under review in 2016. There was majority support, but not consensus, for use of tumor treatment fields therapy as an adjunct to maintenance treatment following initial therapy for glioblastoma multiforme. There was mixed support for the use of tumor treatment fields as an alternative to chemotherapy in advanced or recurrent glioblastoma multiforme.

#### Practice Guidelines and Position Statements

National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2018) include recommendations for the treatment of glioblastoma (see Table 11).<sup>3</sup> For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate methylguanine-DNA methyltransferase promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric field therapy is a category 1 recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a category 2B recommendation.

**Table 11. Guidelines for Adjuvant Treatment of Glioblastoma, by Age and Performance Status**

Age, y	KPS Score,%	Treatment Options	Category
≤70	≥60	· Standard RT plus concurrent and adjuvant temozolomide plus TTF · Standard RT plus concurrent and adjuvant temozolomide	1
≤70	<60	· Hypofractionated RT with/without concurrent or adjuvant temozolomide · Temozolomide · Palliative/best supportive care	2A
>70	≥60	· Hypofractionated RT plus concurrent and adjuvant temozolomide · Standard RT plus concurrent and adjuvant temozolomide plus TTF · Temozolomide alone · Hypofractionated brain RT alone	1
>70	<60	· Hypofractionated brain RT alone · Temozolomide alone · Palliative/best supportive care	2A

KPS: Karnofsky Performance Status; RT: radiotherapy; TTF: tumor treating fields.

#### U.S. Preventive Services Task Force Recommendations

Not applicable.

#### Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 12. Of particular note are the phase 3 trials evaluating TTF therapy in non-small-cell lung cancer and pancreatic cancer. TTF therapy is an active area of research for mechanisms underlying its effects on cancer cells.

**Table 12. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
NCT01971281 <sup>a</sup>	A Phase II Study of TTFields (150 kHz) Concomitant With Gemcitabine and TTFields Concomitant With Gemcitabine Plus Nab-paclitaxel for Front-line Therapy of Advanced Pancreatic Adenocarcinoma	40	Dec 2017 (ongoing)
NCT01894061 <sup>a</sup>	A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma	40	Dec 2018
NCT02663271 <sup>a</sup>	A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFields and Pulsed Bevacizumab Treatment in Patients With Bevacizumab-refractory Recurrent Glioblastoma	18	Mar 2019
NCT02831959 <sup>a</sup>	Pivotal, Open-label, Randomized Study of Radiosurgery With or Without Tumor Treating Fields (TTFields) (150kHz) for 1-10 Brain Metastases From Non-small Cell Lung Cancer (NSCLC) (METIS)	270	Jul 2019
NCT02973789 <sup>a</sup>	LUNAR: Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields) Concurrent With Standard of Care Therapies for Treatment of Stage 4 Non-small Cell Lung Cancer (NSCLC) Following Platinum Failure	534	Dec 2021
NCT02743078 <sup>a</sup>	Phase II Trial Of Optune® Plus Bevacizumab In Bevacizumab-Refractory Recurrent Glioblastoma	85	Aug 2022
NCT03377491 <sup>a</sup>	EF-27 Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields, 150kHz) Concomitant With Gemcitabine and Nab-paclitaxel for Front-line Treatment of Locally-advanced Pancreatic Adenocarcinoma (PANOV-3)	556	Dec 2022

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.]

Horizon BCBSNJ Medical Policy Development Process:

This Horizon BCBSNJ Medical Policy (the "Medical Policy") has been developed by Horizon BCBSNJ's Medical Policy Committee (the "Committee") consistent with generally accepted standards of medical practice, and reflects Horizon BCBSNJ's view of the subject health care services, supplies or procedures, and in what circumstances they are deemed to be medically necessary or experimental/ investigational in nature. This Medical Policy also considers whether and to what degree the subject health care services, supplies or procedures are clinically appropriate, in terms of type, frequency, extent, site and duration and if they are considered effective for the illnesses, injuries or diseases discussed. Where relevant, this Medical Policy considers whether the subject health care services, supplies or procedures are being requested primarily for the convenience of the covered person or the health care provider. It may also consider whether the services, supplies or procedures are more costly than an alternative service or sequence of services, supplies or procedures that are at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the relevant illness, injury or disease. In reaching this conclusion, the Committee considers generally accepted standards of medical practice. The Committee reviews and considers the following: all credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, physician and health care provider specialty society recommendations, the views of physicians and health care providers practicing in relevant clinical areas (including, but not limited to, the prevailing opinion within the appropriate specialty) and any other relevant factor as determined by applicable State and Federal laws and regulations.



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 NoveTTF  
 Novo TTF  
 Optune System

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**Codes:**

(The list of codes is not intended to be all-inclusive and is included below for informational purposes only. Inclusion or exclusion of a procedure, diagnosis, drug or device code(s) does not constitute or imply authorization, certification, approval, offer of coverage or guarantee of payment.)

CPT\*

HCPCS

A4555  
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# Electric Tumor Treatment Fields



## Medical Coverage Policy

Effective Date: 02/22/2018

Revision Date: 02/22/2018

Review Date: 02/22/2018

Policy Number: HCS-0517-006

Page: 1 of 7

Change Summary: Updated Description, Medical Terms, References

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### Disclaimer

State and federal law, as well as contract language, including definitions and specific inclusions/exclusions, take precedence over clinical policy and must be considered first in determining eligibility for coverage. Coverage may also differ for our Medicare and/or Medicaid members based on any applicable Centers for Medicare & Medicaid Services (CMS) coverage statements including National Coverage Determinations (NCD), Local Medical Review Policies (LMRP) and/or Local Coverage Determinations. Refer to the [CMS website](#). The member's health plan benefits in effect on the date services are rendered must be used. Clinical policy is not intended to pre-empt the judgment of the reviewing medical director or dictate to health care providers how to practice medicine. Health care providers are expected to exercise their medical judgment in rendering appropriate care. Identification of selected brand names of devices, tests and procedures in a medical coverage policy is for reference only and is not an endorsement of any one device, test or procedure over another. Clinical technology is constantly evolving, and we reserve the right to review and update this policy periodically. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any shape or form or by any means, electronic, mechanical, photocopying or otherwise, without permission from Humana.

### Description

Electric tumor treatment fields (ETTFs) are created by low-intensity, alternating intermediate frequency (200 kilohertz [kHz]) electric currents which are delivered to a malignant tumor site via insulated electrodes placed around the region of the body containing the tumor.

ETTF treatment first received US Food and Drug Administration (FDA) approval for monotherapy of adults (22 years age or older) with histologically- or radiologically-confirmed recurrent supratentorial glioblastoma (also known as glioblastoma multiforme [GBM] or World Health Organization [WHO] grade IV astrocytoma) following chemotherapy *after* surgery and radiation treatments have been exhausted. The FDA expanded the approval to treat individuals with newly diagnosed GBM when given along with the chemotherapy drug temozolomide following standard treatments that include surgery, chemotherapy and radiation therapy.



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For information regarding **temozolomide**, please refer to Temodor (temozolomide) Pharmacy Coverage Policy.

Reportedly, the application of ETTFs to the surface of the scalp disrupts the rapid division of cancer cells within the brain while sparing nonproliferating brain tissue and the normal rate of cell division. An example of a FDA approved ETTF device includes, but may not be limited to, Optune (formerly known as the Novo TTF-100A System).

The Optune system is a portable battery operated device. Treatment parameters are preset by the device manufacturer and no electrical output adjustments are available to individuals; however, they must learn to change and recharge depleted batteries. Individuals carry the device with them to receive continuous treatment, typically recommended for at least 18 hours per day for four weeks. Electrodes must be replaced every few days and the scalp reshaved in order to maintain optimal contact.<sup>9</sup>

ETTFs are being studied as an adjunctive therapy for additional indications which include, but may not be limited to, breast cancer, lung cancer and pancreatic adenocarcinoma. **(Refer to Coverage Limitations section)**

Treatment planning software (eg, NovoTAL) is available and designed to be utilized prior to ETTF treatment. The software purportedly allows the physician to individualize treatment by determining optimal placement of the transducer arrays based on the individual's most recent magnetic resonance imaging (MRI) scan, head size and tumor location.<sup>2</sup> **(Refer to Coverage Limitations section)**

## Coverage Determination

**All requests for electric tumor treatment fields require review by a medical director.**

Humana members may be eligible under the Plan for **ETTFs** for the following indications:

- Absence of any contraindication listed in the Coverage Limitations section; **AND**
- 22 years of age or older; **AND**
- Combined ETTF and temozolomide in individuals with histologically-confirmed newly diagnosed GBM limited to the supratentorial region following maximal

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debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy<sup>9</sup>; **OR**

- Monotherapy for individuals diagnosed with histologically- or radiologically - confirmed recurrent GBM limited to the supratentorial region following treatment with chemotherapy *after* surgical and radiation treatments have been exhausted<sup>9</sup>

*Coverage  
Limitations*

Humana members may **NOT** be eligible under the Plan for **ETTFs** for any indications other than those listed above including, but may not be limited to:

- If the following contraindications are present:
  - Active implanted medical device (eg, deep brain stimulators, spinal cord stimulators, pacemakers, defibrillators); **OR**
  - Bullet fragments; **OR**
  - Pregnancy; **OR**
  - Shunts; **OR**
  - Skull defects (eg, missing bone with no replacement)<sup>9</sup>; **OR**
- Treatment of other malignant tumors (eg, breast, lung, pancreas)

This is considered experimental/investigational as it is not identified as widely used and generally accepted for any other proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for **treatment planning software** for use with ETTFs (eg, NovoTAL). This is considered experimental/investigational as it is not identified as widely used and generally accepted for the proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.



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**Background** Additional information about **glioblastoma** may be found from the following websites:

- [American Cancer Society](#)
- [National Comprehensive Cancer Network](#)
- [National Library of Medicine](#)

**Medical Alternatives** Physician consultation is advised to make an informed decision based on an individual's health needs.

**Provider Claims Codes** Any CPT, HCPCS or ICD codes listed on this medical coverage policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
64999	Unlisted procedure, nervous system	Not Covered if used to report any procedure outlined in Coverage Limitations section
CPT® Category III Code(s)	Description	Comments
No code(s) identified		
HCPCS Code(s)	Description	Comments
A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only	
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type	

Click [here](#) to view ICD-10-CM code(s) associated with this medical coverage policy.

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<b>Medical Terms</b>	<p><b>Adenocarcinoma</b> – A form of cancer that involves cells from the lining of the walls of many different organs of the body.</p> <p><b>Adjunct</b> – Something joined or added to another thing but not essentially a part of it.</p> <p><b>Astrocytoma</b> – A tumor that begins in the brain or spinal cord in small, star-shaped cells called astrocytes.</p> <p><b>Debulking</b> – Surgically removing all or most of the substance of a tumor or lesion without removing it entirely.</p> <p><b>Electrode</b> – Electrical lead or wire through which current may flow.</p> <p><b>Glioblastoma Multiforme</b> – A malignant rapidly growing central nervous system (CNS) tumor.</p> <p><b>Histologically-Confirmed</b> – The diagnosis of cancer has been confirmed by examining some of the cancerous tissue under a microscope.</p> <p><b>Malignant</b> – Characterized by uncontrolled growth; cancerous, invasive or metastatic.</p> <p><b>Monotherapy</b> – Therapy that uses one type of treatment, such as radiation therapy or surgery alone, to treat a certain disease or condition.</p> <p><b>Palliative</b> – Reducing the intensity of a disease; ease without curing.</p> <p><b>Proliferate</b> – To increase in number or spread rapidly and often excessively.</p> <p><b>Radiation Therapy</b> – Cancer treatment in which high levels of energy rays (X-rays) are used to destroy or shrink cancer cells.</p> <p><b>Supratentorial</b> – Relating to, occurring in, affecting or being the tissues overlying the tentorium cerebelli.</p> <p><b>Temozolomide</b> – A drug that is used for treating cancer, which interferes with the development of cancer cells, slowing their growth and spread in the body.</p>
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**Tentorium Cerebelli** – Arched fold of dura mater that separates the two major parts of the brain, the cerebrum above from the cerebellum below.

**Tumor** – Abnormal growth of tissue resulting from uncontrolled, progressive multiplication of cells and serving no physiological function; a neoplasm.

**WHO Classification of Central Nervous System (CNS) Tumors** – Uses molecular parameters in addition to histology to define many tumor entities, which formulates a concept of how CNS tumor diagnoses should be structured in the molecular era. Grading helps to understand the aggressiveness or malignancy of a tumor.

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## Commercial Medical Policy



### Medical Policy Bulletin

Title: Tumor Treating Fields

Policy #: 07.03.26

The below medical or claim payment policy is applicable to the Company's commercial products only. Policies that are applicable to the Company's Medicare Advantage products are accessible via a separate [Medicare Advantage policy database](#).

The Company makes decisions on coverage based on Policy Bulletins, benefit plan documents, and the member's medical history and condition. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Medical Policy Bulletin document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged or new medical literature may have been published. This Medical Policy Bulletin will be reviewed regularly and be updated as scientific and medical literature becomes available. For more information on how Medical Policy Bulletins are developed, go to the About This Site section of this Medical Policy Web site.

#### Policy

Coverage is subject to the terms, conditions, and limitations of the member's contract.

MEDICALLY NECESSARY



## NEWLY DIAGNOSED GLIOBLASTOMA WHEN USED IN ADJUVANT TREATMENT

TTFIELDS are medically necessary and, therefore, covered for adult individuals (22 years of age or older) with newly diagnosed glioblastoma, when the individual meets all of the following criteria:

- Histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma)
- Tumor located in the supra-tentorial region of the brain
- Karnofsky Performance Score above 60
- Completed standard therapeutic options, such as maximum safe debulking surgery, concomitant temozolomide, or radiotherapy
- TTFIELDS is prescribed with adjuvant temozolomide (maintenance)
- Willingness to use the TTFIELDS device daily for at least 18 hours

## RECURRENT GLIOBLASTOMA WHEN USED AS A MONOTHERAPY

Alternating electric tumor treating fields (TTFIELDS) are medically necessary and, therefore, covered when used as a monotherapy for adult individuals (22 years of age or older) with recurrent glioblastoma, when the individual meets all of the following criteria:

- Histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma)
- Tumor located in the supra-tentorial region of the brain
- Karnofsky Performance Score above 60
- Completed standard therapeutic options, such as maximum safe debulking surgery or systemic chemotherapy or irradiation
- Willingness to use the TTFIELDS device daily for at least 18 hours

## NOT MEDICALLY NECESSARY

TTFIELDS are considered not medically necessary and, therefore, not covered because the available published peer-reviewed literature does not support their use for the treatment of individuals with glioblastoma who have any of the following: an implanted pacemaker, programmable shunts, defibrillator, deep brain stimulator, other implanted devices in the brain, documented clinically significant arrhythmias, or evidence of increased intracranial pressure.

## EXPERIMENTAL/INVESTIGATIONAL

All other uses of TTFIELDS are considered experimental/investigational and, therefore, not covered because their safety and/or effectiveness cannot be established by review of the available published peer-reviewed literature.

## REQUIRED DOCUMENTATION

The Company may conduct reviews and audits of services to our members regardless of the participation status of the provider. Medical record documentation must be maintained on file to reflect the medical necessity of the care and services provided. These medical records may include but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

## PRESCRIPTION (ORDER) REQUIREMENTS

Before submitting a claim to the Company, the supplier must have on file a timely, appropriate, and complete order for each item billed that is signed and dated by the professional provider who is treating the member. Requesting a provider to sign a retrospective order at the time of an audit or after an audit for submission as an original order, reorder, or updated order will not satisfy the requirement to maintain a



timely professional provider order on file.

#### PROOF OF DELIVERY

Medical record documentation must include a contemporaneously prepared delivery confirmation or member's receipt of supplies and equipment. The medical record documentation must include a copy of delivery confirmation if delivered by a commercial carrier and a signed copy of delivery confirmation by member/caregiver if delivered by the DME supplier/provider. All documentation is to be prepared contemporaneous with delivery and be available to the Company upon request.

#### CONSUMABLE SUPPLIES (WHEN APPLICABLE)

The durable medical equipment (DME) supplier must monitor the quantity of accessories and supplies an individual is actually using. Contacting the individual regarding replenishment of supplies should not be done earlier than approximately seven days prior to the delivery/shipping date. Dated documentation of this contact with the individual is required in the individual's medical record. Delivery of the supplies should not be done earlier than approximately five days before the individual would exhaust their on-hand supply.

If required documentation is not available on file to support a claim at the time of an audit or record request, the durable medical equipment (DME) supplier may be required to reimburse the Company for overpayments.

#### Guidelines

Tumor treating fields (TTFields) for the treatment of newly diagnosed and/or recurrent glioblastoma (GBM) utilizes a portable battery or power supply operated device which produces alternating electrical fields within the human body. TTFields are applied to individuals by electrically insulated surface transducer arrays. TTFields disrupt the rapid cell division exhibited by cancer cells.

TTFields are intended to harness electric fields to arrest the proliferation of tumor cells and to destroy them. The TTFields technology takes advantage of the special characteristics and geometrical shape of dividing cells, which make them susceptible to inhibiting cellular division during mitosis. The fields are said to alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used in the treatment of GMB has been specified to 200kHz.

#### KARNOFSKY PERFORMANCE STATUS (KPS)

A scale measuring the ability of individuals to perform ordinary tasks. KPS scores range from 0 to 100; a higher score means a person is better able to carry out daily activities.

KPS	Definition
100	Normal; no complaint; no evidence of disease
90	Able to carry on normal activity; minor signs of symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly



## NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network® (NCCN®), a not-for-profit alliance of 27 leading cancer centers devoted to patient care, research, and education, is dedicated to improving the quality, effectiveness, and efficiency of cancer care so that patients can live better lives. NCCN® promotes the importance of continuous quality improvement and recognizes the significance of creating clinical practice guidelines appropriate for use by patients, clinicians, and other health care decision-makers. NCCN® provides a clinical practice guideline appropriate for use in the treatment of glioblastoma, both as a new diagnosis and in recurrent disease.

NCCN® provide clinical practice guidelines for central nervous system cancers on a variety of prognostic factors, such as: age, good performance status (KPS≥60), MGMT promotor status (methylated or unmethylated/indeterminate). When the medically necessary criteria listed in this medical policy are met, the NCCN® clinical practice guidelines endorse the use of TTFields, as follows:

### IN THE TREATMENT OF NEWLY DIAGNOSED GLIOBLASTOMA

Maximum resection + carmustine (BCNU) wafer with adjuvant treatments inclusive of standard brain RT (recommended dose is 60 Gy in 2.0 Gy fractions or 59.4 Gy in 1.8 Gy fractions) + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy.

### IN THE TREATMENT OF RECURRENT GLIOBLASTOMA

Resection with or without carmustine (BCNU) wafer AND palliative/best supportive care if poor performance, or systemic chemotherapy, or consider reirradiation (category 2B) or alternating electric field therapy for glioblastoma (category 2B).

## REGULATORY STATUS

On April 8, 2011, the FDA gave premarket approval for the NovoTTF-100A system (NovoCure Inc. Portsmouth, New Hampshire) for the treatment of adult patients (22 years of age or older) with histologically confirmed glioblastoma multiforme (GBM), following histologically or radiologically confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

On October 5, 2015, the FDA expanded approval for Optune™ (formerly NovoTTF-100A) system for the treatment of adult patients with newly diagnosed, supra-tentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

## BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, TTFields are covered as durable medical equipment (DME) under the medical benefits of most of the Company's products when the medical necessity criteria listed in this medical policy are met.

## Description

Glioblastoma multiforme (GBM) is the most prevalent and most fatal malignant brain tumor in adults, accounting for nearly 15% of all brain cancers. GBMs account for 46.6% of all malignant tumors with 12,150 new cases predicted annually. Malignant gliomas are histologically heterogeneous and invasive tumors that are derived from neuroglia, or glial cells, whose primary responsibility is to support the central



nervous system's neuron cells. GBMs are classified by the World Health Organization (WHO) as astrocytoma. The WHO provides a grading scale based on the most malignant regions of the tumors. Tumor grades depend upon degree of nuclear atypia, mitotic activity, microvascular proliferation, and necrosis, with increased anaplasia, corresponding to higher tumor grades. The 2007 WHO classification of GBM is a grade IV, indicating the most severe cancer grade, exhibiting rapid tumor growth leading to exceedingly poor prognosis. Eighty percent of individuals diagnosed with GBM will progress to recurrent disease, even after the initial surgical options have been exhausted. Survival expectancy for individuals with newly diagnosed GBM averages between 14.6 to 16.7 months with one-year survival rates of 35%. Following a GBM recurrence, the one-year survival rate is only approximately 20%, and median survival ranges from three to nine months.

Although the prognosis is dismal, the treatment options remain limited. The standard first-line treatment for a GBM is maximum surgical resection of the tumor. The National Comprehensive Cancer Network (NCCN®) has developed clinical practice guidance for the treatment of GBM. At present, the recommended treatment for an individual who is newly diagnosed with a histologically confirmed GBM is: maximum resection surgery, followed by radiotherapy (fractionated focal irradiation in daily fractions of 2 Gray [Gy] given 5 days per week for 6 weeks, for a total of 60 Gy). Gray is a unit of measurement for ionized radiation defined by the absorption of one joule of radiation per one kilogram of matter. In addition to radiotherapy, individuals are treated with concomitant continuous daily temozolomide (75 mg per square meter of body-surface area per day, 7 days per week from the first to the last day of radiotherapy), then subsequent cycles (6) of adjuvant temozolomide (150 to 200 mg per square meter for 5 days during each 28-day cycle). For disease recurrence, standard care includes surgical resection in combination with Gliadel® Wafer, stereotactic radiosurgery, and re-operation for additional tumor resection. Irrespective of the varying treatment protocols between the newly diagnosed and recurrent populations, GBM reoccurrence is still 80% and two-year survival rates remain a mere 27% following initial diagnosis. Acknowledging these dismal treatment outcomes, research has been conducted on new therapeutic agents for the treatment of glioblastoma. Stupp et al developed a new technology called tumor treating fields (TTFields) initially utilized and studied to treat the population with recurrent GBM disease.

TTFields is a technology utilizing electric activity through fields and currents to influence the of polarity of molecules, ions, and the cell membranes found in biological organisms to exert an effect on cellular process and impact cell division. By exposing cancer cells to alternating electric fields of low intensity and intermediate frequency, cellular polarity and ionic energy could be manipulated. This mechanism of action purported by TTFields (alternating electric fields) could selectively arrest cellular division (cytokinesis) in cancer cells by impairing normal mitosis and cytokinesis. TTFields are shown to have no effect on non-dividing cells, but to induce apoptosis in dividing cells. The electric fields interfere with cell division by causing misalignment of highly polarized subunits (microtubule monomers) in the mitotic spindle during the metaphase to anaphase transition and by dielectrophoretic movement of intracellular macromolecules and organelles during telophase. During cytokinesis, TTFields generate non-uniform intracellular fields, pulling organelles towards the neck that separates the newly forming daughter cells. In addition, TTFields interfere with the formation of the mitotic spindle by exerting forces on the charged tubulin subunits. Both processes lead to cell apoptosis and tumor growth inhibition. TTFields exert maximal effects when aligned to a cell's mitotic axis. As a cell's mitotic axis can occur randomly in any direction, additive cytotoxic effects are also observed when TTFields are applied in multiple sequential directions.

Individuals who utilize this technology for the treatment of GBM would need to place four transducer arrays onto their shaved scalp and connected to a portable, battery or power supply operated device (Optune, formerly the NovoTTF-100A system), which is preset to generate 200 kHz electric fields within the brain in two sequentially, perpendicular directions. The intensity of the field is also preset by the manufacturer at >0.7 V/cm. Treatment is intended to be continuous and take place in the home setting to allow the participants to maintain daily activities. Transducer arrays are supplied sterile, and prior to placement of the arrays, the scalp must be shaved carefully to limit the adverse effects (i.e., skin irritation, skin wounding).



Although uninterrupted treatment is recommended, individuals can take treatment breaks of up to an hour, twice per day, for personal needs (i.e., shower).

The electrodes themselves are made from high dielectric constant insulated ceramic discs soldered to a flexible circuit board. The flexible printed circuit incorporates the components required for delivering the current for each ceramic plate and for measuring the temperature. At the set parameters, the electrodes are not reported to cause significant heating due to dielectric losses of the insulation or induced fields in the target tissue.

The Optune system contains a separate software component for the use of clinical treatment planning. The NovoTAL™ system is a workstation based software tool that uses MRI head morphology, tumor size and location measurements, and tissue dielectric properties to optimize the TTFields' distribution and intensity within the tumor by determining the specific region of the brain to treat with the placement of paired arrays. The planning software is intended for use by physicians certified to prescribe electronic TTFields used for the treatment of GBM.

#### PEER REVIEWED LITERATURE

Kirson et al (2004) evaluated 11 types of cancerous cell lines in more than 500 in vitro culture dishes. The researchers calculated growth rates of the cells and measured cell proliferation. In all cell lines reviewed, each culture dish was exposed to TTFields for a period of 24-hour intervals at 100 kHz (at an intensity of 1.0–1.4 V/cm), which resulted in significant inhibition of cell proliferation. To test the relationship between TTFields' intensity and inhibition of cell proliferation, Kirson et al exposed mouse melanoma and rat glioma cell lines to TTFields of different intensities between 1 and 2.5 V/cm. Furthermore, authors reported that the inhibitory effect of TTFields on cell proliferation increased as intensity increased until complete proliferation arrest was achieved at intensities of 1.4 and 2.25 V/cm in melanoma and glioma cells, respectively. The authors reported on the most relevant findings regarding the prolongation of mitosis, stating in treated cells, mitosis seemed to begin normally but was prolonged for variable periods of time before completing cleavage into two daughter cells. In the 500 cells evaluated, the authors reported TTFields had exemplary effect on the cellular process. In the cells treated with TTFields, mitosis was not complete within the standard 3 hours. TTFields treated cells displayed proliferation arrest, and mitosis lasted on average  $124 \pm 91$  min (mean Standard Deviation [SD],  $n = 53$ ; 40–541 min), whereas in the controlled cells, the average mitosis duration was  $62 \pm 8$  min from cell rounding to cytokinesis with a mean SD of 12 and a range of 47–78 minutes. Their findings resulted in statistically significant prolongation of mitosis ( $P < 0.01$ , Mann-Whitney U test).

The authors reported in vivo studies with two animal tumor models. TTFields were generated between implanted (intra-dermal) wholly insulated wires placed on both sides of the tumor. The researchers placed two sets of paired identical insulated wires on the back of a mouse. The comparative in the mouse study was that only one of the pairs were connected to device, thus only exposing the area under the connected pair to TTFields treatment.

The researchers demonstrated that 100 KHz to 1 MHz alternating direction fields have significant specific effects on dividing cells. They reported that the areas treated with electric field of alternating direction provided evidence that all charges and polar molecules are subjected to forces of alternating direction so that ionic flows and dipole rotation oscillate. The basis of these effects during cytokinesis was shown to be that the unidirectional forces induced by disrupting mitotic spindle formation could result in physical disruption of the cell membrane and ultimately to apoptosis. During mitosis, exposure of cells to those fields results in one-fourth being destroyed as the formation of the cleavage furrow approached complete cell separation and violent membrane protrusions and cells exhibit disruption of microtubule spindle elements. Additionally, the authors reported that the direction of the placed electrical current dictates the magnitude of cellular disruption. Kirson et al concluded that when TTFields are placed parallel to the plane division, cells



exhibited more mitotic failure. Placement of the TTFields arrays is an important instruction when the technology is indicated in the treatment of cancers.

#### TUMOR TREATING FIELDS FOR THE TREATMENT OF RECURRENT, SUPRA-TENTORIAL GLIOBLASTOMA MULTIFORME

Kirson et al 2007 evaluated a single arm, pilot trial study on the safety and efficacy of TTFields treatment that was performed on 10 participants with recurrent GBM. Efficacy analysis was performed for recurrent GBM persons focusing on time to disease progression (TTP), progression-free survival at 6 months (PFS6), and overall survival (OS) as the primary outcomes for individuals treated with the NovoTTF-100A device. Based on such a small sample size no statistical hypothesis tests were measured. This study measured progression-free survival at 6 months (PFS6), producing a result of 50% (23–77%; 95% confidence interval). Ninety-five percent confidence intervals of survival proportions were calculated using Kaplan–Meier survival curves. The initial pilot study reported two of the ten participants surviving beyond the follow-up period, with the longest participant living for 124.0 weeks, differing from historical averages.

The authored indicated that the pilot study demonstrated TTP and OS values that were more than double the reported historical medians, and reported that TTFields treatment resulted in one complete response which was tumor free, confirmed by MRI ten months after stopping treatment, and one partial response which was still responding seven months after stopping treatment. Both were still progression free two years from treatment initiation. In addition, one participant had minimal response, and four had stable disease for over 4 months before progressing, with the authors suggesting that the device could conceivably halt tumor growth.

The seminal trial, which led to the Food and Drug Administration (FDA) granting approval of TTFields, was a prospective randomized, phase III trial (EF-11) conducted by Stupp et al. (2012). The EF-11 trial assessed TTFields as a monotherapy, without chemotherapy, compared to physician's standard chemotherapy. 237 participants were randomly assigned in a 1:1 ratio to receive either TTFields, (n=120) or an active control entailing the best available chemotherapy prescribed at the local investigator's discretion (n= 117). Participants were all at least 24 years old, with an average age of 54, had Karnofsky performance scores of  $\geq 70$  with limited other comorbidities. The study design reported that participants would receive baseline examinations and be tested monthly in laboratory. Magnetic resonance imaging (MRI) exams were repeated every second month, and quality of life questionnaires were completed every third month. The researchers allowed any number of prior treatments or recurrences of disease without limits. More than 85% of trial participants had failed two or more prior lines of chemotherapy (i.e.,  $\geq$  second recurrence), and nearly 20% had failed (or had a recurrence) while being treated with bevacizumab prior to enrollment. Tumor response and progression were determined by a blinded central radiology review. This study was designed to demonstrate device superiority over the pharmaceutical control.

The trial's primary outcome was overall survival (OS). Secondary endpoints were: progression-free survival (PFS), the percentage of individuals alive and progression-free at 6 months (PFS6), 1-year survival rate, radiological response rate (RR), quality of life, and safety. OS and PFS were computed from randomization until event or censored at last follow-up utilizing Kaplan–Meier survival method, with 2-sided log rank statistics for comparison. The study had an 80 percent power at a significance level of 0.05 to detect a 60 percent increase in median OS (Hazard Ratio [HR] 0.63). All analyses were performed using the intent to treat population of all randomized participants, individuals lost to follow-up were censored at the time of last contact. Treatment compliance limitations were disproportionately observed in the study as only 78% (93/120) completed one full cycle of the TTFields. Nearly a quarter of all participants in the TTFields treatment arm were noncompliant and discontinued, or failed to begin treatment. 113 of 117 participants (97%) in the active control group started chemotherapy, and all but one person completed one full treatment course. The study presented with follow-up limitations. Twenty-one participants randomized to the control group failed to return to the treatment site, limiting information on disease progression and



toxicity. Moreover, quality of life, a secondary outcome of the study, was only available for assessment on 63 or 27% of trial participants.

Compliance was recorded for those individuals in the TTFields arm who began treatment (n=116) by device downloads. The downloads recorded the treatment duration that TTFields therapy was delivered to each participant. The observed median compliance rate was 86 percent (41–98%) during each treatment month, resulting into a mean duration use of 20.6 hours per day. The study acknowledged variance among the level of disease progression (i.e., first recurrence versus multiple) by the participants but failed to produce comparisons amongst the control groups. Missing these comparisons limits the study's ability to determine the overall effectiveness of the TTFields as a monotherapy. Participants received either single agent or a combination of chemotherapeutic regimens. The percentage breakdown for the chemotherapy agents prescribed were as follows: individuals received bevacizumab (31%), or irinotecan (31%), followed by nitrosoureas (25%), carboplatin (13%), temozolomide (11%) or various other agents (5%). However, the study reported that among individuals treated with the active chemotherapy control, survival was not significantly affected by the choice of chemotherapeutic agent ( $p = 0.66$ ).

The statistical analysis of the survival data was tested for proportional hazards and the assumption of proportionality met using the Cox proportional hazards regression model. The Cox model was performed in two steps; first, all protocol pre-specified baseline variables were tested directly for interactions with OS; then a reduced model was performed testing the effect of all variables with significant interaction ( $p < 0.05$ ) with OS together on the treatment effect of TTFields versus active chemotherapy. At a median follow-up of 39 months, 220 trial participants had succumbed to their disease (93%). The primary endpoint failed to demonstrate a significant increase in mean overall survival between the two treatments. Median survival failed to report statistical significance but was marginally higher in the TTFields group compared to active control chemotherapy (6.6 versus 6.0 months, respectively). One-year survival proportion was 20% in both groups and was unable to demonstrate superiority over common chemotherapy treatments. The 2- and 3-year survival rates were reported as 8% (95% CI, 4-13) and 4% (95% CI, 1-8) versus 5% (95% CI, 3-10) and 1% (95% CI, 0-3) for TTFields versus active control, respectively. The reported hazard ratio was 0.86 (95% CI, 0.66-1.12) in favor of TTFields ( $p = 0.27$ ), indicating that TTFields may be at least equivalent and trending toward an improvement as compared to active chemotherapy. The trial failed to report statistically significant device superiority. Participants were not restricted based on prior treatments or recurrences. Many of the participants presented with advanced disease at trial initiation. As many as 40% of participants were included after the third disease occurrence, possibly decreasing the potential benefit from treatment. Trial results showed TTFields as a monotherapy provided similar, not superior, efficacy as best physician's choice chemotherapy in individuals afflicted with recurrent GBM, albeit superior quality of life and less toxicity resulting from treatment with chemotherapy.

Secondary trial outcomes were presented without adjustment. Quality of life measures were assessed using the QLQ-C30 questionnaire with brain-specific module (BN-20), and the measurements were presented as the change from baseline to 3 months for each of the subscale domains and symptoms scale. The researchers reported that both cognitive and emotional functioning were higher in the TTFields group compared to the chemotherapy group, with no difference in global health. The researchers reported that more objective radiological responses (partial and complete responses) were seen in the TTFields group than in the active control chemotherapy group (14 versus 7, respectively). Progression-free survival (PFS) resulted marginally in favor of participants in the TTFields treatment group, with median PFS reported as 2.2 and 2.1 months for TTFields versus the active control group, respectively (HR 0.81, 95% CI 0.60 - 1.09; log rank  $p = 0.16$ ). Authors state progression-free survival at 6 month was 21.4 percent (95% CI 13.5 - 29.3) in the TTFields group and 15.1 percent (95% CI 7.8 - 22.3) in the active control group (chi squared  $p = 0.13$ ). The authors were unable to claim statistical significance for the trial outcomes.

This study was limited by the inability to be blinded, which could introduce bias and compromise the quality of life assessments. Participant knowledge of their active participation limits the pinnacle prognostic factor



by creating bias. The disproportionate dropout rates are concerning. Many individuals stopped treatment prior to completing one month of treatment duration, and these individuals failed to be treated long enough to make substantial contributions to assist with determinations on device effectiveness. High rates of participant cross-over from chemotherapy into device treatment were observed in the study. Due to the nature of this disease and the dismal prognosis for individuals in this patient population, even marginal changes in overall survival and any increase in quality of life are clinically significant findings, as alternative to the current treatment modalities for individuals with recurrent GBM. Based on the slight improvement, trends observed in this trial suggest that treatment with TTFields may be considered an option.

Kanner et al performed a post hoc analysis to study the intent-to-treat (ITT) population in the TTFields treatment versus the best physician's choice chemotherapy. The authors report overall survival was significantly affected by duration that the TTFields device was worn. Not surprising, since this treatment is without a half-life and would require continuous application of the device to demonstrate a reduction in tumor growth. Stratifying population size to augment the desired results, the post hoc analysis measured outcomes within the population who fully completed at least one cycle (four weeks) of TTFields treatment. Based on those modifications, the researchers observed individuals who complied with treatment protocol of  $\geq 18$  hours daily ( $n=92$ ) had significantly longer overall survival medians, 7.7 versus 4.5 months than those who used treatment  $\leq 18$  hours ( $n=28$ ). Small sample sizes in the study diminish this power of the analysis, and the device may create adherence bias. However, a therapeutic response resulting in an observed mean overall survival increase of three months supports treatment effectiveness when compliance of the treatment protocol is adhered to.

A Patient Registry Dataset (PRiDe) followed 457 persons with recurrent GBM who received TTFields therapy was studied by Mrugala et al in a real-world, phase IV setting. Additional information on the safety and effectiveness of the therapy was assessed in the dataset. The primary outcome of the registry evaluated median overall survival, tolerability of the device, participant compliance and survival, and other prognostic factors. Mrugala reported overall survival (OS) and treatment using Kaplan-Meier methods and Cox proportional hazards model assessed participant characteristics and disease prognostic factors on survival. Evaluation was conducted with log-rank tests to compare OS and daily compliance, prior debulking surgery, Karnofsky Performance Score (KPS), number of recurrence, and prior bevacizumab use.

Overall survival between the PRiDe participants and those treated in the the seminal study with TTFields therapy, and physician's best chemotherapy, increased from 9.6 versus 6.6 versus 6.0 months, respectively. Overall survival rates at one- and two- years increased when compared to treatment arms (TTFields and chemotherapy) from the EF-11 study and PRiDe. As stated above, evidence supported daily compliance as a prognostic factor in TTFields therapy. Participants who achieved the recommended daily compliance of  $\geq 18$  hours a day had significantly longer ( $p=.0001$ ) overall survival --- 13.5 months versus 4.0 months when individuals reported less than  $\leq 18$  hours. Subgroup analysis of individuals treated at first recurrence ( $n=152$ ) demonstrated the longest median overall survival, resulting in 20 months. The overall survival reported in the first recurrence population is similar to more recent studies on the newly diagnosed, suggesting that TTFields may be an option as an effective therapy in GBM recurrence, if treatment is initiated at earliest recurrence.

The registry failed to evaluate participant use of combination therapy with TTFields and prescription programs, such as chemotherapy and anti-vascular endothelial growth factor agents. Outside of a clinical trial, the lack of recording information on other medical management regimens for participants resulted in critically missed analyses in demonstrating the effectiveness of TTFields as a therapy, potentially misrepresenting the true effectiveness of the device in the largest studied population. The registry highlights compliance as a key finding, supporting the adaptation of TTFields; however, it failed to record compliance data for more than one-third of all device users. Device safety and tolerability was proven outside of observational settings. Consistent with other trials, the adverse event most commonly observed



was associated with device-related skin irritation.

The registry presented with limitations, including lack of quality of life measures, as these were excluded in the real world follow-up, an important prognostic factor in overall health outcome from the original trial. Heterogeneity limitations exist within the registry as 67% of the total population were male (n=309), possibly significant considering the need to shave a user's scalp for successful placement of the treatment arrays when utilizing this device.

## TUMOR TREATING FIELDS FOR THE TREATMENT OF NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME

Stupp et al. 2015 conducted a multi-center, open-label, randomized phase III trial designed to evaluate the efficacy and safety of TTFIELDS following chemoradiation with temozolomide (TMZ) for treatment of newly diagnosed glioblastoma. The trial enrolled 695 participants with histologically confirmed supra-tentorial glioblastoma, who were progression-free following debulking surgery or biopsy, and who have completed standard concomitant chemoradiotherapy with TMZ. These individuals were randomized (2:1) to receive combination therapy of TTFIELDS plus temozolomide (TMZ) (n=466) or standard maintenance chemotherapy alone using TMZ (n=229). Randomization was stratified by participant characteristics: degree of resection, and O6-methylguanine-DNA methyltransferase (MGMT) methylation status. The primary outcome was progression-free survival (PFS) in the intent-to-treat (ITT) population and was assessed by independent reviewers (80% power; hazard ratio [HR], 0.78; allowing for 10% loss to follow-up; 2-sided  $\alpha$  level of 0.05). This study investigated shifted overall survival to a secondary outcome but with equal power (HR, 0.76; 2-sided  $\alpha$  = 0.05). To avoid an increase in the risk of a false positive result, overall survival was to only be tested statistically if the PFS was achieved.

In October, 2014, a safety monitoring committee reviewed the findings of an interim analysis reporting on the first 315 participants enrolled in the TTFIELDS plus temozolomide (n=210) and temozolomide (n=105) treatment groups. Pre-specified endpoints were achieved in the intent-to-treat population. After a median follow-up of 38 months (18-60 months), the median PFS in the TTFIELDS plus TMZ arm was 7.1 months from randomization (95% confidence interval [CI], 5.9 - 8.2 months) compared to 4.0 months (95% CI, 3.3 - 5.2) in the control group ([HR] 0.62; 98.7% CI, 0.43 - 0.89; stratified log-rank, P= 0.001). Overall survival in the per-protocol analysis also showed significant improvement. The combination therapy group (n=196) resulted in median OS of 20.5 months (95% CI, 16.7 - 25.0 months) compared to 15.6 months (95% CI, 13.3 - 19.1 months) in the TMZ alone group (n=84) ([HR], 0.64; 99.4% CI, 0.42 - 0.98; P =0.004). Based on the results of the interim analysis, the trial was terminated, and participants in the control group were allowed to receive TTFIELDS. The termination resulted in eleven individuals in the interim analysis and twenty-six participants overall to cross over and receive TTFIELDS treatment. The study demonstrated the addition of TTFIELDS to temozolomide treatment increased median progression-free survival in the ITT population by 3.1 months.

Per the study design, if tumor progression occurred, second-line chemotherapy was offered by local investigator's practice. Noteworthy, TTFIELDS would continue in the treatment arm, until the second radiological confirmed progression, or clinical deterioration, for a maximum of 24 months. Brain imaging was routinely performed, initially at baseline with contrast-enhanced magnetic resonance imaging (MRI) at two weeks prior to treatment initiation, then in two-month intervals until second radiologically confirmed progression in all study participants. Two-thirds of the TTFIELDS plus TMZ group (n=141) continued treatment with TTFIELDS beyond first tumor progression. The trial design to stop at second tumor progression may have clinical importance when considering the progression of disease and the use of TTFIELDS as a treatment option for individuals transitioning from a new diagnosis into recurrent GBM.

The authors reported median treatment duration of 5.8 months (1 - 58 months) with TTFIELDS. Three-quarters (n=157) of enrollees receiving TTFIELDS adhered to therapy. Protocol adherence was considered



wearing the device  $\geq 18$  hours per day on average during the first 3 treatment months. Further analyses in the ITT population showed the median overall survival was 19.6 months (95% CI, 16.6 - 24.4 months) in the TTFields plus temozolomide group compared to 16.6 months (95% CI, 13.6 - 19.2 months) in the temozolomide alone group ([HR], 0.74 95% CI, 0.56 - 0.98; stratified log-rank  $P=0.03$ ). The percentage of those affected by GBM alive at 2 years following enrollment was 43% in the TTFields plus temozolomide group and 29% in the TMZ alone group ( $P=0.006$ , a 14% increase of participants alive at two years in the treatment arm).

The original publication (interim analysis) of the EF-14 study was limited by the investigators stopping the trial earlier and allowing participant cross over. The interim analysis was completed after the initial 315 enrollees reached 18 month follow-up. The results in the initial per-protocol population only evaluated 196, 84 participants in the combination therapy (TTFields plus TMZ) or the TMZ alone arms, respectively. Additionally, as an open-label trial, no sham or placebo treatment was available for the control group. Investigators deemed the use of sham to be unethical, and impractical, and therefore the potential power of a placebo cannot be assessed. This may introduce adherence bias. The researchers acknowledge placebo bias would be unlikely to influence overall survival and progression-free survival. Following the original trial, which reported results that failed to provide evidence of statistically significant improvements in median overall survival, the primary study outcome shifted between the two seminal trials. In the original EF-11 trial, the primary endpoint was overall survival, and in this trial researchers adjusted the primary outcome to progression-free survival. The results of this study on newly diagnosed GBM, the addition of TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and improved overall survival.

Stupp et al 2017 reported on the final analysis inclusive of the entire trial population ( $n=695$ ) from the open-label, randomized phase III trial designed to evaluate the effect of TTFields plus temozolomide (TMZ) versus maintenance TMZ alone on survival for individuals with glioblastoma. Stupp et al previously published the results from an interim analysis on the first 395 participants of the same study. The primary outcomes were consistent to the interim analysis.

The data set was locked on December 28, 2016, and the authors reported median treatment duration of 8.2 months (1 - 82 months) with TTFields. After a medium follow-up of 40 months (34 - 66 months), the median progression-free survival was 6.7 months (95% CI, 6.1 - 8.1 months) for individuals treated with combination therapy versus 4.0 months (95% CI, 3.8 - 4.4 months) for those treated with TMZ alone ([HR] 0.63, 95% CI, 0.52 - 0.76;  $P < 0.001$ ). The secondary outcome reported median overall survival duration of 20.9 months from randomization (95% CI, 19.3 - 22.7 months) in the TTFields plus TMZ group versus 16.0 months (95% CI, 14.0 - 18.4 months) for TMZ only ([HR], 0.63; 95% CI, 0.53 - 0.76;  $P < 0.001$ ). Both were found to be statistically and clinically significant. Analyzing the percentage of living participants over selected time periods from randomization resulted in 46% alive at 2 years, 26% alive at 3 years, and 13% alive at 5 years in the combination therapy arm, compared to the TMZ only arm reporting 31% alive at 2 years ( $p < 0.001$ ); 16% at 3 years ( $P=0.009$ ); and 5% at 5 years ( $P=0.004$ ). Significant percentage increases across each selected time period favoring adjuvant TTField therapy.

The median time to randomization was equal among the treatment arms with 3.8 month (range 1.7 - 6.2) and 3.7 months (range, 1.4 - 6.3) in the combination therapy, and the TMZ alone treatment groups, respectively. Kaplan-Meier estimates for survival were accessed at 6 months for the rate of progression-free survival between the two treatment groups. The authors reported on progression-free survival at 6 months as 56% (95% CI, 51% - 61%) for the TTFields group and 37% (30% - 44%) with TMZ only ( $P < 0.001$ ). Cox proportional hazards analyzed both overall survival and progression-free survival across factors: trial arms, age, sex, MGMT status, location, and county of residence. Results using Cox proportional hazards with 95% confidence intervals demonstrated several prognostic factors significantly improved OS; these prognostic factors include: TTFields treatment group (HR, 0.63, 0.53 - 0.76,  $P < 0.001$ ), female sex (HR, 0.76, 0.63 - 0.92,  $P = 0.005$ ), MGMT status (HR, 0.50, 0.41 - 0.62;  $P < 0.001$ ), younger age



(measured continuously, [HR], 0.978 per year, 0.969 - 0.985;  $P < 0.001$ ), and higher KPS (as a categorical variable in 10 point increments  $P < 0.001$ ).

Interestingly, fifty-five percent of participants had a gross tumor resection (95% of tumor removed) and 13% had only a biopsy performed, results indicating the extent of excision was not statistically significant when investigating overall survival ( $P = 0.183$ ). The addition of TTFields was not associated with an increase in systemic adverse events (AE) (48% versus 44%;  $P = 0.58$ ). Higher rates of AE found in the TTFields treated group were attributed to longer duration of TMZ treatment in the experimental group as a result of delayed disease progression. Investigators report inclusive criteria for TTFields treatment utilizing Karnofsky Performance Score (KPS). KPS is a scale measuring the ability of individuals to perform ordinary tasks. KPS scores range from 0 to 100; a higher score means a person is better able to carry out daily activities. The author reported time to sustain 10 point reduction in KPS significantly longer for the combination group versus the group treated with only TMZ (5.5 months; 95% CI, 5.0 - 6.3 months versus 3.9 months; 95% CI, 3.1 - 5.2 months, respectively; [HR], 0.80; 95% CI, 0.67 - 0.95;  $P = 0.009$ ).

Potentially important for future studies, a small majority of the experimental population (51%;  $n = 237$ ) continued TTFields treatment beyond first treatment progression. The investigators may want to evaluate, in the newly diagnosed population who elect to continue TTFields as a combination therapy beyond first progression, whether significant improvements are observed in progression-free survival and OS compared to the outcomes of the historical recurrent population. The recurrent population only has the option to utilize TTFields as a monotherapy. The largest study to date utilizing the TTFields technology presented with similar limitations as observed in the interim analysis (no sham, burden of use when utilizing the device). Another limitation in the final analysis was that quality of life data points were not recorded. Also, participant heterogeneity limitations exist since nearly 70% of the study participants were male and 89% were white.

The final analysis for the treatment of glioblastoma utilizing the TTFields technology demonstrated that the combination therapy of TTFields and temozolomide chemotherapy following standard concomitant TMZ and radiotherapy has shown to significantly improve progression-free survival and overall survival in the newly diagnosed population.

NovoCure Inc. of Portsmouth, New Hampshire (subsidiary of NovoCure Ltd., Haifa, Israel) was granted approval for the NovoTTF-100A system. The NovoTTF-100A Treatment Kit received US Food and Drug Administration (FDA) Premarket Approval on April 8, 2011 (P100034). The current supplement Optune™ System, which received FDA Premarket Approval on October 5, 2015 (P1000034/S013) was submitted to expand the indications for use: Optune™ System with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supra-tentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

In summary, TTFields has been demonstrated to be a safe and effective alternative treatment, and should be considered for individuals with either recurrent or newly diagnosed Glioblastoma. In 2015, The National Comprehensive Cancer Network® (NCCN®) clinical practice guidelines appropriateness in the treatment of central nervous system cancer for use of TTFields has shifted to consider category 3 in the recurrent population as a category 2B. A 2B category allows providers to consider the use of TTFields in treatment of recurrent disease. The NCCN® 2016 guidelines classifies alternating electronic fields therapy as a 2A grade for newly diagnosed glioblastoma individuals. NCCN® guidelines demonstrate TTFields used in concomitant treatment with adjuvant temozolomide following radiotherapy and concomitant temozolomide for the newly diagnosed. Indicating that use of TTFields could be used an initial treatment therapy, when prescribed with adjuvant temozolomide.

#### TUMOR TREATING FIELDS IN OTHER INDICATIONS

Researchers have initiated evaluations utilizing NovoCure's TTFields technology in the treatment of other



solid tumor indications. The various populations actively being investigated include cancers such as: non-small cell lung (NSCLC), brain metastases (1-5; 1-10) from NSCLC, pancreatic, ovarian, mesothelioma, and high grade glioma and ependymoma in children. Each of these separate indications has been either recently completed or is actively being studied in phase II trials to determine safety and efficacy with this new modality. The trials range in size, n= 5 in the child study to 82 participants in the mesothelioma trial. Variance exists between the primary outcomes researched in each of the new indications. In the ovarian and pancreatic cancers, the primarily investigated outcome was device related adverse effects and feasibility based on compliance as a result of the individual's early discontinuation of treatment. The tumor location could be a factor in compliance. Toxicity was the principal measurement in the non-small cell lung cancer study, whereas overall survival was the primary outcome in the mesothelioma trial. All studies listed time to progression, or progression-free survival as a secondary endpoint.

Non-small cell lung cancer is currently under investigation, with participants actively enrolled into a prospective, randomized controlled phase III trial aimed to test the efficacy and safety of TTFields in combination with PD-1 inhibitors or docetaxel as a second-line treatment. The researchers will assess the overall survival of participants with the TTFields and docetaxel or PD-1 inhibitors versus docetaxel or PD-1 alone in a superiority study design. Interestingly, if the primary outcome fails, the researchers will evaluate overall survival of those treated with TTFields and docetaxel versus PD-1 inhibitors alone in a separate, more challenging non-inferiority study. This study has a completion date of December 2020.

Evaluation of a trial on the feasibility of Optune for children with recurrent or progressive supra-tentorial high-grade glioma and ependymoma cancers was initiated in early 2017. This trial aims to demonstrate use of the Optune device as a feasible treatment option in the pediatric population and report treatment-related toxicities assessed by Common Terminology Criteria for Adverse Events v4.0. A total of 25 children are expected to participate in this trial. This study was the first trial, inclusive of the pivotal trials, that utilizes the TTFields technology that was not funded or sponsored by the device manufacture, NovoCure, Ltd. The pediatric study is sponsored by Pediatric Brain Tumor Consortium, with support from the National Cancer Institute (NCI).

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## Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility , benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply .

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company .

The Coding T able lists any CPT , ICD-9, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear .

➤ CPT Procedure Code Number(s)

N/A

Professional and outpatient claims with a date of service on or before September 30, 2015, must be billed using ICD-9 codes. Professional and outpatient claims with a date of service on or after October 1, 2015, must be billed using ICD-10 codes.



Facility/Institutional inpatient claims with a date of discharge on or before September 30, 2015, must be billed with ICD-9 codes. Facility/Institutional inpatient claims with a date of discharge on or after October 1, 2015, must be billed with ICD-10 codes.

➤ ICD - 10 Procedure Code Number(s)

N/A

Professional and outpatient claims with a date of service on or before September 30, 2015, must be billed using ICD-9 codes. Professional and outpatient claims with a date of service on or after October 1, 2015, must be billed using ICD-10 codes.

Facility/Institutional inpatient claims with a date of discharge on or before September 30, 2015, must be billed with ICD-9 codes. Facility/Institutional inpatient claims with a date of discharge on or after October 1, 2015, must be billed with ICD-10 codes.

➤ ICD -10 Diagnosis Code Number(s)

C71.0 Malignant neoplasm of cerebrum, except lobes and ventricles

C71.1 Malignant neoplasm of frontal lobe

C71.2 Malignant neoplasm of temporal lobe

C71.3 Malignant neoplasm of parietal lobe

C71.4 Malignant neoplasm of occipital lobe

C71.5 Malignant neoplasm of cerebral ventricle

C71.8 Malignant neoplasm of overlapping sites of brain

➤ HCPCS Level II Code Number(s)

A4555 Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only

E0766 Electrical stimulation device used for cancer treatment, includes all accessories, any type

➤ Revenue Code Number(s)

N/A

## Policy History

07.03.26:

03/23/2018	This new policy has been issued to communicate the Company's coverage position.
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Version Effective Date: 03/23/2018

Version Issued Date: 03/23/2018

Version Reissued Date: N/A



**Kaiser Foundation Health Plan  
of Washington**

## Clinical Review Criteria

### Tumor Treating Fields Therapy

**NOTICE:** Kaiser Foundation Health Plan of Washington and Kaiser Foundation Health Plan of Washington Options, Inc., provide these Clinical Review Criteria for internal use by their members and health care providers. The Clinical Review Criteria only apply to Kaiser Foundation Health Plan of Washington and Kaiser Foundation Health Plan of Washington Options, Inc. Use of the Clinical Review Criteria or any Kaiser Permanente entity name, logo, trade name, trademark, or service mark for marketing or publicity purposes, including on any website, or in any press release or promotional material, is strictly prohibited.

Kaiser Permanente Clinical Review Criteria are developed to assist in administering plan benefits. These criteria neither offer medical advice nor guarantee coverage. Kaiser Permanente reserves the exclusive right to modify, revoke, suspend or change any or all of these Review Criteria, at Kaiser Permanente's sole discretion, at any time, with or without notice. **Member contracts differ in their benefits. Always consult the patient's Medical Coverage Agreement or call Kaiser Permanente Customer Service to determine coverage for a specific medical service.**

## Criteria

### For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	<a href="#">Tumor Treatment Fields Therapy (L34823)</a>
Medical Director Article	<a href="#">Tumor Treatment Field Therapy (TTFT) – Response to Comments</a>

### For Non-Medicare Members

- I. Tumor-treating fields (TTF) to treat primary (not recurrent) supratentorial glioblastoma multiforme (GBM) may be considered medically necessary when **ALL of the following** are met:
  - A. Patient is 18 years of age or older; and
  - B. Karnofsky Performance Status\* is 70% or higher; and
  - C. Documentation of histologically-confirmed primary glioblastoma multiforme; and
  - D. Patient has completed standard concomitant chemoradiation with temozolomide(TMZ); and
  - E. Disease did not progress through chemo radiation (possible "pseudo progression" does not exclude patients from receiving TTF) and
  - F. TTF will be administered concurrently with TMZ, unless TMZ has been ineffective, not tolerated, or is contraindicated and
  - G. TTF must be started no later than 60 days from the end of chemo radiation
- II. Continued treatment of TTF can be covered until the second radiological progression ( meaning 2 consecutive images showing tumor progression) or clinical deterioration

**All authorizations are for 90 days. Re-authorizations require updated clinical notes and imaging.**

\*Karnofsky Performance Status Scale

Condition	Value (%)	level of Functional Capacity
Able to carry on normal activity and to work; no special care needed	100%	No complaints; no evidence of disease
	90%	Able to carry on normal activity; minor signs or symptoms of disease
	80%	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70%	Cares for self; unable to carry on normal activity or to do active work
	60%	Requires occasional assistance but is able to care for most personal needs
	50%	Requires considerable assistance and



		frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; diseases may be progressing rapidly	40%	Disabled; requires special care and assistance
	30%	Severely disabled; hospital admission indicated although death not imminent
	20%	Very sick; hospital admission necessary; active supportive treatment necessary
	10%	Moribund; fatal processes progressing rapidly
	0%	Dead

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, KPWA will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations..

## Background

Glioblastoma (GBM), an incurable disease, has the highest incidence rate (3.19/100,000 population) amongst the central nervous system (CNS) tumors with an average survival of 15 months (Thakkar et al., 2014). Numerous genetic and environmental risk factors have been investigated but none is associated with a large population of GBM (Wrensch, Minn, Chew, Bondy, & Berger, 2002). The median age of diagnosis is 64 years and GBM is frequently found in the supratentorial region (Adams et al., 2013). GBM is an aggressive malignancy with poor prognosis and low survival. The first year relative survival rate is 35% and this estimate decreases over time (Ostrom et al., 2013) making the long term survival very harsh. Standard treatment consists of resection with combination of radiation and chemotherapy. These therapies, whether combined or utilized alone, do not significantly decrease mortality and do not lack adverse effects. Because GBM infiltrates the brain, it is prone to recurrence. Management of recurrence became challenging and therefore indispensable for better clinical outcomes. Different therapeutic options have been investigated but tumor treating fields (TTFields), a novel treatment, seems comparable to standard chemotherapy including Temozolomide and is less toxic (Roger Stupp et al., 2012).

TTFields, developed by NovoCure Ltd, is a medical device for the treatment of recurrent GBM. It is a portable, non-invasive, battery-operated and wearable device that disrupts the division of cancer cells and proliferation in the supratentorial region by delivering low-intensity and intermediate frequency (200 kHz) alternating electric fields via transducer arrays applied to the scalp by means of hypoallergenic ceramic disks, which are placed on the scalp using Hydrogel (Axelgaard Manufacturing Co, Ltd, Fallbrook, CA) as a conductor; It is believed that TTFields inhibits cytokinesis and microtubule assemble, and therefore inhibiting growth and causing death of cancer cells (Butowski, Wong, Mehta, & Wilson, 2013). The NovoTTF-100A received premarket approval from the Food and Drug Administration (FDA) on April 10, 2011 for treatment in adult patients with confirmed GBM, following confirmed recurrence in an upper region of the brain after receiving chemotherapy. The device is intended to be used independently and as an alternative to standard medical therapy after surgical and radiation options have been exhausted (FDA 2011).

The review of the safety and effectiveness of TTFields Therapy for the treatment of recurrent GBM in adults has been reviewed previously. However, it is being reviewed based on a request from the Clinical Review Unit with a focus on the combination of TTFields plus Temozolomide as maintenance therapy on newly diagnosed GBM. It is also being reviewed for coverage decision support.

## Medical Technology Assessment Committee (MTAC)

### Tumor Treatment Fields Therapy

#### 08/19/2013: MTAC REVIEW

**Evidence Conclusion:** The randomized phase III trial sought to compare the overall survival of subjects treated with the NovoTTF-100A alone to subjects treated with the best standard of care (BSC) chemotherapy available for recurrent GBM (Stupp, Wong et al. 2012). In the clinical study, 237 subjects with previously diagnosed GBM who experienced recurrence of their tumor or their condition worsened despite conventional therapy (surgery and chemo-radiotherapy followed by chemotherapy) were randomly assigned to receive either NovoTTF-100A stand-alone treatment or the BSC chemotherapy (as determined by the local physician). The primary endpoint for the



study was overall survival, as assessed by the log-rank test in the intent-to-treat population. In addition, the study examined the safety and tolerability of NovoTTF-100A treatment based on the incidence and severity of adverse events and toxicities. Secondary endpoints measured in the study included the progression free survival rate at 6 months, time to progression, one year survival rate, quality of life and radiological response rate. The ITT population includes all subjects who were randomized to the trial. At a median follow up of 39 months 93% of patients had died. The analysis was performed by the treatment group to which the subject was randomized. The study results showed that overall survival with the NovoTTF-100A System was no superior to that seen with active best standard of care chemotherapy. There was a slightly higher incidence of neurological adverse events in the NovoTTF-100A treated group (43.1%) compared to the best standard of care control group (36.3%). Mild to moderate skin irritation beneath the device electrodes was seen in 16% of NovoTTF-100A-treated subjects. NovoTTF-100A treated subjects experienced a lower frequency of the classic adverse events as seen with chemotherapy (such as gastrointestinal, hematological and infectious adverse events) with the best standard of care. Quality of life surveys indicated an improved quality of life in the NovoTTF-100A recurrent GBM subjects compared to the best standard of care recurrent GBM subjects. The trial was generally well designed and conducted with recruitment from 28 different clinics, randomization and minimal loss to follow up. Limitations identified by the authors include the somewhat heterogenous patient population with patients included after progression of one or several lines of prior chemotherapy. The authors also observed that the study could have benefited from a placebo or treatment-free control arm. Some limitations that are not highlighted by the authors include the decreasing number of subjects remaining after 12 months which may limit the ability to reliably estimate the long term survival outcomes. Furthermore, it is important to note that the primary investigator, as well as a number of other authors had financial and professional ties with the manufacturer of the device Novocure Ltd., Rye Beach, New Hampshire. Although the study failed to show that the NovoTTF-100A treatment is superior to chemotherapy with respect to overall survival the NovoTTF-100A treatment exhibits minimal toxicity, has clinically comparable primary and secondary effectiveness and better quality of life compared to the chemotherapies used in the control arm of the study.

**Articles:** A literature search was conducted revealing a small pilot trial and one larger pivotal study. The pilot study was an open-label prospective single arm study to assess the safety and effectiveness of TTFields for the treatment of GBM. The pivotal study was prospective, open label, best standard of care randomized control trial to compare the overall survival of subjects treated with NovoTTF-100A alone to subjects treated with the best standard of care chemotherapy available for recurrent GBM. In addition, the search revealed a case study illustrating one patient's success with TTFields therapy and one expert opinion article discussing the concept, evidence and future of TTFields. The clinical study that formed the FDA's basis for determining that the NovoTTF-100A System is safe and effective for its intended use was selected for review: Stupp R, Wong ET, Kanner AA, Steinberg D, Engelhard H, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomized phase III trial of a novel treatment modality. *European Journal of Cancer*. 2012;48, 2192-2202. See [Evidence Table](#).

The use of TT Fields Therapy does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

### ***Tumor Treating Fields plus Temozolomide as maintenance therapy for Glioblastoma Multiforme (GBM)***

#### **03/21/2016: MTAC REVIEW**

**Evidence Conclusion:** The previous review on TTFields, completed in 2013, aimed to determine the safety and efficacy of TTFields therapy compared to standard medical therapy, for the treatment of recurrent GBM for adult patients. The study evaluating NovoTTF-100A versus Physician Choice Chemotherapy in recurrent glioblastoma (Roger Stupp et al., 2012) was reviewed and no improvement in overall survival was identified. The author of the review concluded that there was insufficient evidence to determine the safety and effectiveness of TTFields Therapy. Stupp, R., S. Taillibert, et al. (2015). "Maintenance Therapy With Tumor-treating Fields plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial." See [Evidence Table 1](#). This randomized phase 3 trial, open label, parallel design, multicenter, (R. Stupp et al., 2015) intended to assess the efficacy and safety of TTFields in combination with temozolomide for treatment of patients with GBM after initial treatment with chemoradiation. After patients were diagnosed, they were initially treated with chemoradiation comprised of Temozolomide and concomitant radiation. Brain MRI was required 2 weeks prior to starting the maintenance treatment (to exclude progression cases). After completion of the initial treatment, patients were randomized at a ratio of 2 to 1 to receive TTFields + Temozolomide (n=466) or Temozolomide alone (n=229). TTFields was initiated within 4-7 weeks from the last dose of concomitant chemoradiotherapy. While Temozolomide was given on a basis of 150-200 mg/m<sup>2</sup>/d for 5 days every 28 days for 6-12 cycles, TTFields was delivered continuously (>18 hours/day) via 4 transducer arrays placed on the shaved scalp and connected to a portable medical device. The primary outcome was progression-free survival (PFS) in the intent-to-treat population (significance level of 0.01) and the secondary outcome was the overall survival (OS) in the per-protocol population (significance level of 0.006). Safety and tolerability were also evaluated. A total of 695 patients were recruited but



the trial was terminated after the interim analysis showed a benefit in Progression Free Survival. This interim analysis was conducted after the first 315 randomized patients reached a minimum of 18-month follow-up. Thus, data from 315 patients with 210 patients in the intervention group and 105 patients in the control group were analyzed. Baseline characteristics were nearly similar across the groups with median age of 57 years. The findings were based on the interim analysis. Patients who were treated with TTFields plus Temozolomide had longer PFS [7.1 months (CI, 5.9 – 8.2)] than those who were treated with Temozolomide alone [4 months (95%CI, 3.3 – 5.2)]. Likewise, patients who were treated with TTFields plus Temozolomide had longer OS [20.5 months (16.7 - 25)] than those who were treated with Temozolomide alone [15.6 months (CI, 13.3 – 19.1)]. In addition, no major increases in toxic effects were associated with the intervention. The most common adverse events were thrombocytopenia, mild to moderate skin irritation, and general disorders. In conclusion, the combination of TTFields plus Temozolomide prolonged PFS as well as OS compared to Temozolomide alone for the maintenance treatment of patients with GBM. However, this is an interim analysis with less than 50% of participation with exclusion of patients with early progression decreasing the quality of the evidence. MTAC will re-review the technology once full data are analyzed. Conclusion: The interim analysis with less than 50% participation suggests that TTF plus Temozolomide may prolong progression-free survival and overall survival versus Temozolomide alone. Nevertheless, the study failed to include patients with severe prognosis, therefore results should be interpreted with cautious. Other pitfalls remain in the open-label nature of the RCT leading to placebo effects and variation in the delivery of chemotherapy and radiochemotherapy.

**Articles:** A literature search was conducted revealing 13 articles (Please refer to appendix B) of which one meets inclusion criteria (studies involving histologically confirmed GBM, standard concomitant chemoradiation with Temozolomide, age >18 years with ≥ 70% on Karnofsky Performance Status (KPS) score and good renal and bone marrow function, received TTFields plus Temozolomide as maintenance therapy). The study on “Maintenance Therapy with tumor-treating fields plus temozolomide vs Temozolomide alone for Glioblastoma: A randomized clinical trial” will be critically appraised.

The use of Tumor Treating Fields (TTFields) plus Temozolomide as maintenance therapy for Glioblastoma multiforme (GBM) does meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Date Created	Date Reviewed	Date Last Revised
10/01/2013	10/01/2013 <sup>MPC</sup> , 10/07/2014 <sup>MPC</sup> , 08/04/2015 <sup>MPC</sup> , 05/03/2016 <sup>MPC</sup> , 04/04/2017 <sup>MPC</sup> , 02/06/2018 <sup>MPC</sup>	09/06/2016

<sup>MPC</sup> Medical Policy Committee

Revision History	Description
03/21/2016	Added MTAC Review for of Tumor Treating Fields (TTFields) plus Temozolomide as maintenance therapy for Glioblastoma multiforme (GBM)
05/03/2016	MPC approved GH developed criteria for Tumor Treating Fields (TTFields)
09/06/2016	Criteria added for continued treatment of TTF
06/28/2017	Added Medical Directors Comments
03/06/2018	MPC approved revised criteria for continued treatment of TTF

## Codes

HCPCS: A4555; E0766




## MEDICAL POLICY – 1.01.29

## Tumor Treating Fields Therapy for Glioblastoma

Effective Date:	Nov. 1, 2017	RELATED MEDICAL POLICIES:
Last Revised:	Oct. 3, 2017	None
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

[POLICY CRITERIA](#) | [CODING](#) | [RELATED INFORMATION](#)  
[EVIDENCE REVIEW](#) | [REFERENCES](#) | [HISTORY](#)

 Clicking this icon returns you to the hyperlinks menu above.

## Introduction

Tumor treating fields (TTF) is a new treatment being studied for use in certain cancers. The therapy consists of low-level electrical currents that arise from small insulated electrodes placed on the skin surface. TTF is believed to cause cell death during a later stage of development. Currently this therapy is covered as one treatment option for people who have a deadly form of brain cancer called glioblastoma multiforme. People wear a helmet with small electrodes attached to the scalp for at least 18 hours per day during TTF therapy. This treatment requires pre-approval by the plan, and this policy describes when this treatment is covered. TTF is considered investigational for other types of cancer (therefore not covered), as there is not yet enough scientific data that shows it works for other diagnoses.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

## Policy Coverage Criteria



Condition	Medical Necessity
<b>Glioblastoma- adjuvant therapy</b>	<p><b>Tumor treating fields (TTF) therapy to treat glioblastoma is medically necessary when ALL of the following are met:</b></p> <ul style="list-style-type: none"> <li>• The patient has completed debulking surgery or biopsy</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• The patient has completed radiation therapy</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• The patient is being treated with temozolmide</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• TTF therapy is begun within 7 weeks of the final radiation treatment</li> </ul>

Condition	Investigational
<b>Glioblastoma- for advanced or recurrent disease</b>	<b>Tumor treating fields therapy(TTF) to treat advanced or recurrent glioblastoma is considered investigational.</b>
<b>All other diagnoses</b>	<b>Tumor treating fields (TTF) is considered investigational for all other indications.</b>

## Coding

Code	Description
<b>HCPCS</b>	
A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

## Related Information





## Evidence Review

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### Background

#### *Glioblastoma Multiforme*

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults. They comprise approximately 15% of all brain and central nervous system tumors, and more than 50% of all tumors that arise from glial cells.<sup>1</sup> The peak incidence for GBM occurs between the ages of 45 and 70 years. GBMs are grade IV astrocytomas, the most deadly type of glial cell tumor, and are often resistant to standard chemotherapy.<sup>1</sup> According to the National Comprehensive Cancer Network, only a third of patients with GBM survive for 1 year and less than 5% live beyond 5 years.<sup>2</sup>

#### *Treatment of Glioblastoma Multiforme*

The primary treatment for initial GBM is debulking surgery to remove as much of the tumor as possible. At that time, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea, or BCNU) impregnated wafer.<sup>2</sup> Depending on the patient's physical condition, adjuvant radiotherapy and/or chemotherapy (typically temozolomide) are sometimes given. After adjuvant therapy, some patients may undergo maintenance therapy with temozolomide.

No standard treatment exists for recurrent GBM. After these initial treatments, additional debulking surgery may be used if recurrence is localized. Other treatment options for recurrent disease include various forms of systemic medications such as bevacizumab and bevacizumab combined with other chemotherapy such as irinotecan, BCNU/chloroethylnitrosourea (CCNU), or temozolomide. Temozolomide, nitrosourea, PCV (a combination of procarbazine, CCNU, and vincristine), cyclophosphamide, and platinum-based agents have also been used.<sup>2</sup> External beam radiotherapy also may be used. Response rates in recurrent disease are less than 10%, and progression-free survival at 6 months is typically less than 20%.<sup>2,3</sup>



## ***Tumor Treating Fields Therapy***

TTF therapy is a new, noninvasive technology intended to treat GBM on an outpatient basis using electrical fields.<sup>3-5</sup> TTF therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis. TTF are proposed to inhibit rapidly dividing tumor cells by two mechanisms: arrest of cell proliferation and destruction of cells while undergoing division.<sup>4,5</sup>

The NovoTTF-100A System has received marketing approval from the U.S. Food and Drug Administration to deliver TTF therapy. TTF therapy via the NovoTTF-100A System is delivered by a battery-powered, portable device that generates the fields via disposable electrodes noninvasively attached to the patient's shaved scalp over the site of the tumor.<sup>3,4</sup> The device is used by the patient at home on a continuous basis (20-24 h/d) for the duration of treatment, which can last for several months. The device is covered under the DME benefit. Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living.<sup>3,4</sup>

## **Summary of Evidence**

For individuals who have progressive or recurrent glioblastoma multiforme (GBM) after initial or repeat surgery, radiotherapy, and/or chemotherapy who then receive tumor treatment fields (TTF) therapy as an alternative to standard chemotherapy, the evidence includes a randomized controlled trial (RCT) and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The published RCT reported no differences in outcomes between patients treated with TTF and with standard chemotherapy. This trial had several methodologic limitations. Comparisons that were made only included an active control of questionable efficacy, which might not reflect current standard of care. There was a high dropout rate (>20% of patients in each group were lost to follow-up) and, for the quality of life outcomes, only 25% of enrolled patients had complete data. The 2 nonrandomized studies were small and had limited validity due to differences in the patient populations treated with TTF and standard care. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have newly diagnosed GBM and receive TTF therapy as an adjunct to standard maintenance therapy following their initial treatment with surgery, radiotherapy, and/or chemotherapy, the evidence includes a single RCT. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The single RCT reported that patients who received TTF treatment plus





temozolomide had longer progression-free survival (3.1 months) and overall survival (4.9 months) than patients who received temozolomide alone. However, the trial had methodologic limitations including the lack of a placebo control, differential dropout between groups, and the possibility of adherence bias for outcomes reported with per-protocol analysis. Further corroboration of these results is needed in high-quality RCTs. Although evidence is limited, NCCN has given this therapy a 2A rating. There are very few treatment options for this disease, and the side effect profile of TTF is much more tolerable to patients.

## Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in [Table 1](#).

**Table 1. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
<a href="#">NCT01894061</a> <sup>a</sup>	A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma	40	Dec 2017
<a href="#">NCT01756729</a> <sup>a</sup>	A Prospective, Non-randomized, Concurrent Control, Open Label, Post-approval Study of NovoTTF-100A in Recurrent GBM Patient	486	Jan 2018
<a href="#">NCT02743078</a> <sup>a</sup>	Phase II Trial Of Optune® Plus Bevacizumab In Bevacizumab-Refractory Recurrent Glioblastoma	85	Apr 2018
<a href="#">NCT01954576</a>	A Phase II Study of the NovoTTF-100A system, Enhanced by Genomic Analysis to Identify the Genetic Signature of Response in the Treatment of Recurrent Glioblastoma Multiforme	30	May 2018
<a href="#">NCT02663271</a> <sup>a</sup>	A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFIELDS and Pulsed Bevacizumab Treatment in Patients With Bevacizumab-refractory Recurrent Glioblastoma	25	May 2018
<a href="#">NCT02893137</a> <sup>a</sup>	Phase 1 Enhancing Optune Therapy of Recurrent Glioblastoma Multiforme Using Targeted Surgical Skull Remodeling	15	Oct 2019



NCT No.	Trial Name	Planned Enrollment	Completion Date
<a href="#">NCT01925573</a> <sup>a</sup>	Proposed Pilot Study of Combined Optune+ Bevacizumab, and Hypofractionated Stereotactic Irradiation for Bevacizumab-Naive Recurrent Glioblastoma	27	Dec 2021

NCT: national clinical trial. <sup>a</sup> Denotes industry-sponsored or cosponsored trial.

## Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may provide appropriate reviewers who collaborate with and make recommendations during this process, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 3 physician specialty societies (one of which provided 6 responses and 2 of which provided 1 response each) and 1 academic medical center (total of 9 individual responses) while this policy was under review in 2016. There was majority support, but not consensus, for use of tumor treatment fields therapy as an adjunct to maintenance treatment following initial therapy for glioblastoma multiforme. There was mixed support for the use of tumor treatment fields as an alternative to chemotherapy in advanced or recurrent glioblastoma multiforme.

## Practice Guidelines and Position Statements

National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2016)<sup>2</sup> include a recommendation for the treatment of glioblastoma. For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate MGMT promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric currents therapy is a category 2A recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a 2B recommendation.





## Medicare National Coverage

There is no National Coverage Decision (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

## Regulatory Status

In April 2011, the NovoTTF-100A™ System (Novocure, Haifa, Israel; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.<sup>7</sup> The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM [glioblastoma multiforme], following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment, and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."<sup>7</sup>

In September 2014, FDA approved Novocure's request to change its product name from NovoTTF-110A System to Optune®.<sup>8</sup>

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.<sup>6</sup> The device was granted priority review status in May 2015 because there was no legally marketed alternative device currently available for the treatment of newly diagnosed GBM that represents a life-threatening condition.

The FDA-approved label reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

Based on the 2011 approval Optune® is also approved for the treatment of recurrent GBM in the supratentorial region of the brain after receiving chemotherapy. The device is intended for use as a monotherapy, and as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

FDA product code: NZK.





## References

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## History

Date	Comments
10/14/13	New Policy. Policy created with literature search through June 3, 2013; considered investigational.





Date	Comments
12/06/13	Update Related Policies. Removed 8.01.31 as it was archived.
11/20/14	Annual Review. Policy updated with literature review through June 26, 2014. References 8 and 16-17 added. Editorial revisions made to rationale section. Policy statement unchanged. New HCPCS codes A9900 and E1399 added to the policy.
10/13/15	Annual Review. Policy updated with literature review through July 8, 2015; references 10-11 removed and 10-12 added. Policy statement unchanged. Removed informational ICD-9 and ICD-10 codes.
09/01/16	Annual Review, approved August 9, 2016. Changed statement to MN when criteria are met.
03/30/17	Coding correction; updated code descriptions. Minor formatting update.
11/01/17	Annual Review, approved October 3, 2017. Policy updated with literature review through June 5, 2017; no references added. Removed HCPCS codes A9900 and E1399. Policy statements rewritten for clarity.

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.







## Discrimination is Against the Law

LifeWise Health Plan of Oregon complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. LifeWise does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

LifeWise:

- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that LifeWise has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals

PO Box 91102, Seattle, WA 98111

Toll free 855-332-6396, Fax 425-918-5592, TTY 800-842-5357

Email [AppealsDepartmentInquiries@LifeWiseHealth.com](mailto:AppealsDepartmentInquiries@LifeWiseHealth.com)

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at

<https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at:

U.S. Department of Health and Human Services

200 Independence Avenue SW, Room 509F, HHH Building

Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Complaint forms are available at

<http://www.hhs.gov/ocr/office/file/index.html>.

## Getting Help in Other Languages

**This Notice has Important Information.** This notice may have important information about your application or coverage through LifeWise Health Plan of Oregon. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-596-3440 (TTY: 800-842-5357).

### አማርኛ (Amharic):

ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ LifeWise Health Plan of Oregon ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀናት ሊኖሩ ይችላሉ። የጤናን ሽፋንዎን ለመጠበቅና በአስፈላጊ እርዳታ ለማግኘት በተወሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎት ይሆናል። ይህን መረጃ እንዲያገኙ እና ያለምንም ከፍተኛ በቋንቋዎ እርዳታ እንዲያገኙ መብት አለዎት። በስልክ ቁጥር 800-596-3440 (TTY: 800-842-5357) ይደውሉ።

### العربية (Arabic):

يحتوي هذا الإشعار معلومات هامة. قد يحتوي هذا الإشعار معلومات مهمة بخصوص طلبك أو التغطية التي تريد الحصول عليها من خلال LifeWise Health Plan of Oregon. قد تكون هناك تواريخ مهمة في هذا الإشعار. وقد تحتاج لاتخاذ إجراء في تواريخ معينة للحفاظ على تغطيتك الصحية أو للمساعدة في دفع التكاليف. يحق لك الحصول على هذه المعلومات والمساعدة بلغتك دون تكبد أية تكلفة. اتصل بـ 800-596-3440 (TTY: 800-842-5357).

### 中文 (Chinese):

**本通知有重要的訊息。**本通知可能有關於您透過 LifeWise Health Plan of Oregon 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-596-3440 (TTY: 800-842-5357)。

### Omoo (Cushite):

**Beeksisi kun odeeffannoo barbaachisaa qaba.** Beeksisti kun sagantaa yookan karaa LifeWise Health Plan of Oregon tiin tajaajila keessan ilaalchisee odeeffannoo barbaachisaa qabaachuu danda'a. Guyyaawwan murteessaa ta'an beeksisa kana keessatti ilaalaa. Tarii kaffaltiidhaan deeggaramuuf yookan tajaajila fayyaa keessaniif guyyaa dhumaa irratti wanti raawwattan jiraachuu danda'a. Kaffaltii irraa bilisa haala ta'een afaan keessaniin odeeffannoo argachuu fi deeggarsa argachuuf mirga ni qabaattu. Lakkoofsa bilbilaa 800-596-3440 (TTY: 800-842-5357) tii bilbilaa.

### Français (French):

**Cet avis a d'importantes informations.** Cet avis peut avoir d'importantes informations sur votre demande ou la couverture par l'intermédiaire de LifeWise Health Plan of Oregon. Le présent avis peut contenir des dates clés. Vous devrez peut-être prendre des mesures par certains délais pour maintenir votre couverture de santé ou d'aide avec les coûts. Vous avez le droit d'obtenir cette information et de l'aide dans votre langue à aucun coût. Appelez le 800-596-3440 (TTY: 800-842-5357).

### Kreyòl ayisyen (Creole):

**Avi sila a gen Enfòmasyon Enpòtan ladann.** Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè LifeWise Health Plan of Oregon. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kèk aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resevwa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rele nan 800-596-3440 (TTY: 800-842-5357).

### Deutsche (German):

**Diese Benachrichtigung enthält wichtige Informationen.** Diese Benachrichtigung enthält unter Umständen wichtige Informationen bezüglich Ihres Antrags auf Krankenversicherungsschutz durch LifeWise Health Plan of Oregon. Suchen Sie nach eventuellen wichtigen Terminen in dieser Benachrichtigung. Sie könnten bis zu bestimmten Stichtagen handeln müssen, um Ihren Krankenversicherungsschutz oder Hilfe mit den Kosten zu behalten. Sie haben das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Rufen Sie an unter 800-596-3440 (TTY: 800-842-5357).

### Hmoob (Hmong):

**Tsaw ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb.** Tej zaum tsaw ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam los ntawm LifeWise Health Plan of Oregon. Tej zaum muaj cov hnub tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas peb kom koj ua tsis pub dhau cov caij nyoog uas teev tseg rau hauv daim ntawv no mas koj thiaj yuav tau txais kev pab cuam kho mob los yog kev pab them tej nqi kho mob ntawd. Koj muaj cai kom lawv muab cov ntshiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-596-3440 (TTY: 800-842-5357).

### Iloko (Ilocano):

**Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion.** Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyonyo wenno coverage babaen iti LifeWise Health Plan of Oregon. Daytoy ket mabalin dagiti importante a petsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramideryo nga addang sakbay dagiti partikular a naituding nga aldaw tapno mapagtalinaedyo ti coverage ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagsasao nga awan ti bayadanyo. Tumawag iti numero nga 800-596-3440 (TTY: 800-842-5357).

### Italiano (Italian):

**Questo avviso contiene informazioni importanti.** Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso LifeWise Health Plan of Oregon. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente. Chiama 800-596-3440 (TTY: 800-842-5357).



**日本語 (Japanese):**

この通知には重要な情報が含まれています。この通知には、LifeWise Health Plan of Oregon の申請または補償範囲に関する重要な情報が含まれている場合があります。この通知に記載されている可能性がある重要な日付をご確認ください。健康保険や有料サポートを維持するには、特定の期日までに行動を取らなければならない場合があります。ご希望の言語による情報とサポートが無料で提供されます。800-596-3440 (TTY: 800-842-5357)までお電話ください。

**한국어 (Korean):**

본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 LifeWise Health Plan of Oregon 를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 본 통지서에는 핵심이 되는 날짜들이 있을 수 있습니다. 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하의 이러한 정보와 도움을 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-596-3440 (TTY: 800-842-5357) 로 전화하십시오.

**ລາວ (Lao):**

ແຈ້ງການນີ້ມີຂໍ້ມູນສໍາຄັນ. ແຈ້ງການນີ້ອາດຈະມີຂໍ້ມູນສໍາຄັນກ່ຽວກັບຄໍາຮ້ອງສະໝັກ ຫຼື ຄວາມຄຸ້ມຄອງປະກັນໄພຂອງທ່ານຜ່ານ LifeWise Health Plan of Oregon. ອາດຈະມີວັນທີສໍາຄັນໃນແຈ້ງການນີ້. ທ່ານອາດຈະຈຳເປັນຕ້ອງດຳເນີນການຕາມກຳນົດເວລາສະເພາະເພື່ອຮັກສາຄວາມຄຸ້ມຄອງປະກັນສຸຂະພາບ ຫຼື ຄວາມຊ່ວຍເຫຼືອເລື່ອງຄ່າໃຊ້ຈ່າຍຂອງທ່ານໄດ້. ທ່ານມີສິດໄດ້ຮັບຂໍ້ມູນນີ້ ແລະ ຄວາມຊ່ວຍເຫຼືອເປັນພາສາຂອງທ່ານໂດຍບໍ່ເສຍຄ່າ. ໃຫ້ໃບທາ 800-596-3440 (TTY: 800-842-5357).

**ភាសាខ្មែរ (Khmer):**

សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរ៉ាប់រងរបស់អ្នកគាមរយ: LifeWise Health Plan of Oregon ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ជ្រាបសមត្ថភាព ដល់កំណត់ថ្លៃជាក់លាក់សំខាន់ ដើម្បីនឹងរក្សាទុកការធានារ៉ាប់រងសុខភាពរបស់អ្នក ឬប្រាក់ជំនួយចេញថ្លៃ។ អ្នកមានសិទ្ធិទទួលព័ត៌មាននេះ និងជំនួយនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-596-3440 (TTY: 800-842-5357)។

**ਪੰਜਾਬੀ (Punjabi):**

ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ LifeWise Health Plan of Oregon ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਜਦਕਿ ਖਾਸ ਤਾਰੀਖਾਂ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀਂ ਜਸਹਤ ਕਵਰੇਜ ਰਿਖਣੀ ਹੋਵੇ ਜਾਂ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਕੱਠ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ ਤੋਂ ਪਹਿਲਾਂ ਕੁੱਝ ਖਾਸ ਕਦਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫਤ ਵਿੱਚ ਤੇ ਆਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-596-3440 (TTY: 800-842-5357).

**فارسی (Farsi):**

این اعلامیه حاوی اطلاعات مهم میباشد. این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق LifeWise Health Plan of Oregon باشد. به تاریخ های مهم در این اعلامیه توجه نمایید. شما ممکن است برای حفظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کارهای خاصی احتیاج داشته باشید. شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-596-3440 (TTY: 800-842-5357) تماس با شماره 800-842-5357 تماس برقرار نمایید.

**Polskie (Polish):**

To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez LifeWise Health Plan of Oregon. Prosimy zwrócić uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-596-3440 (TTY: 800-842-5357).

**Português (Portuguese):**

Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do LifeWise Health Plan of Oregon. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-596-3440 (TTY: 800-842-5357).

**Română (Romanian):**

Prezenta notificare conține informații importante. Această notificare poate conține informații importante privind cererea sau acoperirea asigurării dumneavoastră de sănătate prin LifeWise Health Plan of Oregon. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistența privitoare la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-596-3440 (TTY: 800-842-5357).

**Русский (Russian):**

Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через LifeWise Health Plan of Oregon. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-596-3440 (TTY: 800-842-5357).

**Fa'asamoa (Samoan):**

Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, LifeWise Health Plan of Oregon, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilo fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'matalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-596-3440 (TTY: 800-842-5357).

**Español (Spanish):**

Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de LifeWise Health Plan of Oregon. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-596-3440 (TTY: 800-842-5357).

**Tagalog (Tagalog):**

Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay maaaring naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng LifeWise Health Plan of Oregon. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-596-3440 (TTY: 800-842-5357).

**ไทย (Thai):**

ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน LifeWise Health Plan of Oregon และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อรักษากារประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือนี้ในภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 800-596-3440 (TTY: 800-842-5357)

**Український (Ukrainian):**

Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страховального покриття через LifeWise Health Plan of Oregon. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-596-3440 (TTY: 800-842-5357).

**Tiếng Việt (Vietnamese):**

Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình LifeWise Health Plan of Oregon. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-596-3440 (TTY: 800-842-5357).



# MEDICA®

## UTILIZATION MANAGEMENT POLICY

**TITLE:** ELECTRIC TUMOR TREATMENT FIELDS

**EFFECTIVE DATE:** November 16, 2016

*This policy was developed with input from specialists in neurosurgery, oncology, and radiation oncology and endorsed by the Medical Policy Committee.*

### IMPORTANT INFORMATION – PLEASE READ BEFORE USING THIS POLICY

*These services may or may not be covered by all Medica plans. Please refer to the member's plan document for specific coverage information. If there is a difference between this general information and the member's plan document, the member's plan document will be used to determine coverage. With respect to Medicare, Medicaid and MinnesotaCare members, this policy will apply unless these programs require different coverage. Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions about this Medica utilization management policy may call the Medica Provider Service Center toll-free at 1-800-458-5512.*

*Medica utilization management policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care and treatment.*

### PURPOSE

To promote consistency between reviewers in utilization management decision-making by providing the criteria that generally determine the medical necessity of electric tumor treatment fields (Optune System). The Coverage Issues box below outlines the process for addressing the needs of individuals who do not meet these criteria.

### BACKGROUND

#### I. Definitions

- A. **Electric Tumor Treatment Fields (ETTF or TTF)** technology applies low-intensity alternating electric fields to the brain to disrupt the division of cancer cells. The Optune system (formerly known as NovoTTF-100A) consists of four sets of insulated electrodes and a generator. The array attaches to the patient's shaved scalp and is connected to the generator by wires. The patient wears the device continuously (20-24 hours per day), for at least four weeks.
- B. **Glioblastoma** also known as GBM, glioblastoma multiforme, and grade IV astrocytoma, is a fast-growing type of central nervous system tumor that forms from glial (supportive) tissue of the brain and spinal cord. Glioblastoma usually occurs in adults and affects the brain more often than the spinal cord. Symptoms depend on tumor location and may include language deficits, numbness, weakness, headaches, seizures, nausea and vomiting, or confusion. It is most common in older individuals, with a median survival rate of approximately 15 months; five-year survival rate is approximately 4%. The exact cause of glioblastoma is not known.
- C. The **NovoTAL simulation software** may be used to determine the optimal location for placement of the transducer array, which is based on the patient's MRI scan, head size, and tumor location.
- D. The **supratentorial** region of the brain is located above the tentorium cerebelli (the arched fold of dura mater that covers the upper surface of the cerebellum and supports the occipital lobes of the cerebrum) and contains the cerebrum.

### MEDICAL NECESSITY CRITERIA

#### I. Indications for electric tumor treatment fields

Documentation in the medical records indicates that **all of the following** criteria are met:

- A. The member is at least 22 years old
- B. There is histologically-confirmed glioblastoma multiforme (GBM)
- C. The treatment is being provided by a certified Novo-TTF 100A System prescriber, and **one of the following**



are met:

1. There is concurrent treatment of new disease with temozolomide (TMZ), unless TMZ has been ineffective, not tolerated, or is contraindicated, OR
2. There is recurrent disease and the treatment used as monotherapy after other options have been exhausted.

II. Contraindications

**None of the following** are present:

- A. An active implantable medical device (e.g., deep brain stimulator, spinal cord stimulator, vagus nerve stimulator, pacemaker, defibrillator, programmable shunt)
- B. Skull defect
- C. Bullet fragment
- D. Known sensitivity to conductive hydrogels used with device transducer arrays
- E. Pregnancy.

COVERAGE ISSUES

1. Prior authorization **is required** for electric tumor treatment fields.
2. Coverage may vary according to the terms of the member's plan document.
3. Electric tumor treatment fields (Optune System) for all other indications, including the treatment of other malignant tumors, *is investigative, and therefore, not covered*.
4. For Medicare members, refer to the Medicare Coverage Database Search Page as applicable, at: <http://www.cms.hhs.gov/mcd/search.asp>
5. If the Medical Necessity and Coverage Criteria are met, Medica will authorize benefits within the limits in the member's plan document.
6. If it appears that the Medical Necessity and Coverage Criteria are not met, the individual's case will be reviewed by the medical director or an external reviewer. Practitioners are reminded of the appeals process in their Medica Provider Administrative Manual.

DOCUMENT HISTORY

Original Effective Date	June 1, 2016
MPC Endorsement Date(s)	March 3, 2016, November 9, 2016

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15. Wong ET, Lok E, Swanson KD. An Evidence-Based Review of Alternating Electric Fields Therapy for Malignant Gliomas. *Curr Treat Options Oncol*. August 2015;16(8):40. doi: 10.1007/s11864-015-0353-5.

**11/2015 MPC:**

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## Medi-Cal Update

Durable Medical Equipment and Medical Supplies | January 2016 | Bulletin 484

### 2. Updated Indications for HCPCS Code E0766

Effective for dates of service on or after February 1, 2016, the indications for the treatment of glioblastoma multiforme (GBM) with HCPCS code E0766 (electrical stimulation device used for cancer treatment, includes all accessories, any type) have been updated.

HCPCS code E0766 is indicated for the treatment of adult patients 22 years of age and older:

- With temozolomide for newly diagnosed, histologically confirmed supratentorial GBM following maximal debulking surgery, and completion of radiation therapy together with concomitant standard of care chemotherapy; or,
- With histologically or radiologically confirmed recurrent GBM in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy and an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

This information is reflected in the following provider manual(s):

Provider Manual(s)	Page(s) Updated
Durable Medical Equipment Pharmacy	<a href="#">dura bil dme (35)</a>



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

<b>Line:</b>	<b>1</b>
Condition:	PREGNANCY (See Guideline Notes 2,4,22,33,39,64,65,85,92,99,147,150,153,175)
Treatment:	MATERNITY CARE
ICD-10:	N88.3,O02.81-O02.89,O09.00-O09.93,O10.011-O10.93,O11.1-O11.9,O12.00-O12.25,O13.1-O13.9,O14.00-O14.95,O15.00-O15.9,O16.1-O16.9,O20.0-O20.9,O21.0-O21.9,O22.00-O22.53,O22.8X1-O22.93,O23.00-O23.43,O23.511-O23.93,O24.011-O24.93,O25.10-O25.3,O26.00-O26.53,O26.611-O26.93,O29.011-O29.93,O30.001-O30.93,O31.00X0-O31.8X99,O32.0XX0-O32.9XX9,O33.0-O33.2,O33.3XX0-O33.9,O34.00-O34.13,O34.211-O34.93,O35.0XX0-O35.9XX9,O36.0110-O36.93X9,O40.1XX0-O40.9XX9,O41.00X0-O41.93X9,O42.00,O42.011-O42.92,O43.011-O43.93,O44.00-O44.53,O45.001-O45.93,O46.001-O46.93,O47.00-O47.9,O48.0-O48.1,O60.00-O60.03,O60.10X0-O60.23X9,O61.0-O61.9,O62.0-O62.9,O63.0-O63.9,O64.0XX0-O64.9XX9,O65.0-O65.9,O66.0-O66.3,O66.40-O66.9,O67.0-O67.9,O68,O69.0XX0-O69.9XX9,O70.0-O70.1,O70.20-O70.9,O71.00-O71.9,O72.0-O72.3,O73.0-O73.1,O74.0-O74.9,O75.0-O75.5,O75.81-O75.9,O76,O77.0-O77.9,O80-O85,O86.11-O86.89,O87.0-O87.9,O88.011-O88.83,O89.01-O89.9,O90.1-O90.6,O90.81-O90.9,O91.011-O91.03,O91.211-O91.23,O92.011-O92.79,O98.011-O98.93,O99.011-O99.89,O9A.111-O9A.53,Q92.61,Q95.0-Q95.1,Z03.71-Z03.79,Z22.330,Z29.13,Z31.82,Z32.00-Z32.02,Z34.00-Z34.93,Z36.0-Z36.5,Z36.81-Z36.9,Z3A.00-Z3A.49,Z39.0-Z39.2,Z86.32,Z87.51-Z87.59
CPT:	01958-01963,01967-01969,12021,12041,12042,13131-13133,37191-37193,57022,58150,58180,58260,58262,58290,58291,58541-58544,58550-58554,58559-58573,59000-59100,59160-59622,59866,59871,74712,74713,76801-76828,76945,76946,80081,81420,81507-81512,84163,84704,88235,88267,88269,93792,93793,96150-96155,97802-97814,98960-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0108,G0109,G0248-G0250,G0270,G0271,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,H0045,S2401-S2403,S2405,S2411,S8055,S9140,S9141,S9208-S9214
<b>Line:</b>	<b>2</b>
Condition:	BIRTH OF INFANT (See Guideline Notes 64,65,153)
Treatment:	NEWBORN CARE
ICD-10:	P00.0-P00.7,P00.81-P00.9,P01.0-P01.9,P02.0-P02.1,P02.20-P02.9,P03.0-P03.6,P03.810-P03.9,P04.0-P04.3,P04.41-P04.9,P05.00-P05.9,P22.1,P29.11-P29.2,P29.4,P29.81-P29.9,P39.3,P92.01-P92.09,P94.1-P94.9,P96.0,P96.3-P96.5,P96.82-P96.89,Q27.0,Z05.0-Z05.3,Z05.41-Z05.9,Z38.00-Z38.8
CPT:	93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99468,99469-99473,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>3</b>
Condition:	PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS (See Coding Specification Below) (See Guideline Notes 1,17,64,65,106,122,140)
Treatment:	MEDICAL THERAPY
ICD-10:	Z00.00-Z00.01,Z00.110-Z00.5,Z00.70-Z00.8,Z01.00-Z01.10,Z01.110-Z01.118,Z01.411-Z01.42,Z08,Z11.1-Z11.4,Z11.51,Z12.11,Z12.2,Z12.31,Z12.4,Z13.1,Z13.220,Z13.4-Z13.6,Z13.820,Z13.88,Z20.1-Z20.7,Z20.810-Z20.89,Z23,Z29.11-Z29.12,Z29.14,Z29.8,Z39.1,Z71.41,Z71.7,Z76.1-Z76.2,Z80.0,Z80.41,Z91.81
CPT:	44392,44394,45333,45338,45384,45385,76706,77067,90378,90460-90472,90620,90621,90630-90674,90680-90688,90696-90716,90723-90736,90739-90748,90750,90756,92002-92014,92551,93792,93793,96110,96150-96155,98966-98969,99051,99060,99070,99078,99173,99188,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS:	D0191,D1206,G0008-G0010,G0104,G0105,G0121,G0248-G0250,G0296,G0297,G0396,G0397,G0438-G0445,G0463-G0468,G0490,G0511,G0513,G0514,H0049,H0050,S0285,S0610-S0613,S9443
	CPT code 96110 can be billed in addition to other CPT codes, such as evaluation and management (E&M) codes or preventive visit codes.
<b>Line:</b>	<b>4</b>
Condition:	SUBSTANCE USE DISORDER (See Guideline Notes 64,65,175)
Treatment:	MEDICAL/PSYCHOTHERAPY
ICD-10:	F10.10-F10.11,F10.20-F10.21,F11.10-F11.11,F11.20-F11.21,F12.10-F12.11,F12.20-F12.21,F13.10-F13.11,F13.20-F13.21,F14.10-F14.11,F14.20-F14.21,F15.10-F15.11,F15.20-F15.21,F16.10-F16.11,F16.20-F16.21,F18.10-F18.11,F18.20-F18.21,F19.10-F19.11,F19.20-F19.21,Z71.51
CPT:	90785,90832-90840,90846-90853,90882,90887,93792,93793,96150-96155,97810-97814,98966-98969,99051,99060,99201-99239,99324-99357,99366,99408,99409,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0410,G0411,G0425-G0427,G0443,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004-H0006,H0010-H0016,H0018-H0020,H0032-H0035,H0038,H2010,H2013,H2033,H2035,T1006,T1007,T1502



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

- Line: 5**  
Condition: TOBACCO DEPENDENCE (See Guideline Notes 4,64,65,92)  
Treatment: MEDICAL THERAPY/BEHAVIORAL COUNSELING  
ICD-10: F17.200-F17.228,F17.290-F17.299,Z71.6,Z72.0  
CPT: 93792,93793,96150-96155,97810-97814,98966-98969,99078,99201-99215,99224,99324-99355,99366,99406,99407,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: D1320,G0248-G0250,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,G9016,H0038,S9453
- Line: 6**  
Condition: REPRODUCTIVE SERVICES (See Guideline Notes 64,65,68,162,176)  
Treatment: CONTRACEPTION MANAGEMENT; STERILIZATION  
ICD-10: Z30.011-Z30.9,Z31.61-Z31.69,Z39.2,Z40.03  
CPT: 11976,11981-11983,55250,57170,58300,58301,58340,58565,58600-58615,58661,58670,58671,58700,74740,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S4981,S4989,T1015
- Line: 7**  
Condition: MAJOR DEPRESSION, RECURRENT; MAJOR DEPRESSION, SINGLE EPISODE, SEVERE (See Guideline Notes 64,65,69,102)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F32.2-F32.5,F32.9,F33.0-F33.3,F33.40-F33.42,F33.9  
CPT: 90785,90832-90840,90846-90853,90867,90868,90870,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99281-99285,99304-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005
- Line: 8**  
Condition: TYPE 1 DIABETES MELLITUS (See Coding Specification Below) (See Guideline Notes 62,64,65,108)  
Treatment: MEDICAL THERAPY  
ICD-10: E10.10-E10.29,E10.311-E10.319,E10.3211-E10.9,E89.1,O24.011-O24.019,Z46.81  
CPT: 49435,49436,90935-90947,90989-90997,92002-92014,92227,92250,93792,93793,95249-95251,96150-96155,97605-97608,97802-97804,98960-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0108,G0109,G0245,G0246,G0248-G0250,G0270,G0271,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9140-S9145,S9353  
  
CPT 95250 and 95251 are included on this line for services related to real-time continuous glucose monitoring but not retrospective (professional) continuous glucose monitoring.
- Line: 9**  
Condition: ASTHMA (See Guideline Notes 64,65,156)  
Treatment: MEDICAL THERAPY  
ICD-10: J45.20-J45.52,J45.901-J45.998,Z51.6  
CPT: 31600,31601,31820,31825,86003,86008,86486,93792,93793,94002-94005,94640,94644-94668,95004,95018-95180,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0424-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9441
- Line: 10**  
Condition: GALACTOSEMIA (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: E74.20-E74.29  
CPT: 93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



*PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)*

- Line: 11**  
Condition: RESPIRATORY CONDITIONS OF FETUS AND NEWBORN (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: P22.0,P22.8-P22.9,P23.0-P23.9,P24.00-P24.9,P25.0-P25.8,P26.0-P26.9,P28.0,P28.10-P28.9,P84,Q31.0,R04.81  
CPT: 31580,33946-33966,33969,33984-33989,39501,39503,39545,93792,93793,94002-94005,94610,94640,94660-94668,94772-94777,96154,96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 12**  
Condition: HIV DISEASE (INCLUDING ACQUIRED IMMUNODEFICIENCY SYNDROME) AND RELATED OPPORTUNISTIC INFECTIONS (See Guideline Notes 7,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: B20,Z21  
CPT: 90284,93792,93793,94642,96150-96155,97810-97814,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 13**  
Condition: CONGENITAL HYPOTHYROIDISM (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: E00.0-E00.9,E03.0-E03.1,P72.0  
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 14**  
Condition: PHENYLKETONURIA (PKU) (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: E70.0-E70.1  
CPT: 93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 15**  
Condition: CONGENITAL INFECTIOUS DISEASES (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A50.01-A50.9,P35.0-P35.9,P37.0-P37.4,P37.8-P37.9  
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 16**  
Condition: LOW BIRTH WEIGHT; PREMATURE NEWBORN (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: P07.00-P07.39,P83.0,P91.60  
CPT: 92227,92228,93792,93793,94772,96154,96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 17**  
Condition: NEONATAL MYASTHENIA GRAVIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: P94.0  
CPT: 93792,93793,96154,96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 18**  
Condition: FEEDING PROBLEMS IN NEWBORNS (See Guideline Notes 64,65,139)  
Treatment: MEDICAL THERAPY  
ICD-10: P78.2,P78.83,P92.1-P92.9,Q38.1  
CPT: 41010,92526,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: D7960,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



*PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)*

**Line: 19**  
Condition: HYDROCEPHALUS AND BENIGN INTRACRANIAL HYPERTENSION (See Guideline Note 65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: G91.0-G91.3,G91.8-G91.9,G93.2,Q03.0-Q03.9,Q04.4-Q04.8,Q05.0-Q05.3,Q07.02-Q07.03,Z45.41  
CPT: 20664,31294,61020,61070,61107,61120,61210,61215,61322,61323,62100,62120,62121,62160-62163,62180-62258,62272,63740-63746,67570,92002-92014,92081-92083,92133,92134,92226,92250,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 20**  
Condition: CYSTIC FIBROSIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: E84.0,E84.11-E84.9  
CPT: 31600,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 21**  
Condition: VESICoureteral REFLUX (See Guideline Notes 64,65,138)  
Treatment: MEDICAL THERAPY, SURGERY  
ICD-10: N13.70-N13.71,N13.721-N13.9,Q62.7  
CPT: 50220,50225,50234-50240,50605,50760-50820,50845,50860,50947,50948,52281,52327,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 22**  
Condition: SCHIZOPHRENIC DISORDERS (See Guideline Notes 64,65,69,82)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F20.0-F20.5,F20.81-F20.9,F25.0-F25.9  
CPT: 90785,90832-90840,90846-90853,90870,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99281-99285,99304-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005

**Line: 23**  
Condition: INTRACRANIAL HEMORRHAGES; CEREBRAL CONVULSIONS, DEPRESSION, COMA, AND OTHER ABNORMAL CERERAL SIGNS OF THE NEWBORN (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: P90,P91.0-P91.1,P91.3-P91.5,P91.811-P91.9  
CPT: 93792,93793,96154,96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 24**  
Condition: ENDOCRINE AND METABOLIC DISTURBANCES SPECIFIC TO THE FETUS AND NEWBORN (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: P70.0-P70.9,P71.0-P71.9,P72.1-P72.9,P74.0-P74.9  
CPT: 93792,93793,96154,96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 25**  
Condition: DYSPLASIA OF CERVIX AND CERVICAL CARCINOMA IN SITU, CERVICAL CONDYLOMA (See Guideline Notes 64,65,66)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: D06.0-D06.9,N84.2,N86,N87.0-N87.9,N88.0,N89.0-N89.4,R87.610-R87.616,R87.810,R87.820,Z87.410  
CPT: 57061,57065,57150,57180,57400,57452-57530,57540,57550-57558,58120,58150,58260-58263,58290,58291,58550-58554,58570-58573,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES  
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- Line: 26**  
Condition: BIPOLAR DISORDERS (See Guideline Notes 64,65,69,82)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F30.10-F30.9,F31.0,F31.10-F31.9  
CPT: 90785,90832-90840,90846-90853,90870,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99281-99285,99304-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,S9537,T1005
- Line: 27**  
Condition: TYPE 2 DIABETES MELLITUS (See Guideline Notes 62,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: E08.00-E08.29,E08.311-E08.319,E08.3211-E08.9,E09.00-E09.29,E09.311-E09.319,E09.3211-E09.9,E11.00-E11.29,E11.311-E11.319,E11.3211-E11.9,E13.00-E13.29,E13.311-E13.319,E13.3211-E13.9,E16.1  
CPT: 48155,90935-90947,90989-90997,92002-92014,92227,92250,93792,93793,96150-96155,97605-97608,97802-97804,98960-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0108,G0109,G0245,G0246,G0248-G0250,G0270,G0271,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9140-S9145,S9353,S9537
- Line: 28**  
Condition: DRUG WITHDRAWAL SYNDROME IN NEWBORN (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: P96.1-P96.2  
CPT: 93792,93793,96154,96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 29**  
Condition: REGIONAL ENTERITIS, IDIOPATHIC PROCTOCOLITIS, ULCERATION OF INTESTINE (See Guideline Notes 9,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: K50.00,K50.011-K50.919,K51.00,K51.011-K51.319,K51.411-K51.413,K51.418-K51.919,K52.3,K62.6,K63.2-K63.3,K92.81,Z46.59  
CPT: 44110,44120-44125,44139-44160,44187-44227,44300-44320,44345,44379,44381,44384,44391,44402,44404,44405,44620-44661,44701,45112-45119,45123,45136,45303,45308-45320,45327,45334,45335,45340,45347,45381,45382,45386,45389,45397,45805,45825,46710,46712,49442,86711,91110,93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 30**  
Condition: EPILEPSY AND FEBRILE CONVULSIONS (See Guideline Notes 64,65,84)  
Treatment: MEDICAL THERAPY  
ICD-10: G40.001-G40.919,R56.00-R56.9  
CPT: 93792,93793,96150-96155,97535,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 31**  
Condition: SEVERE BIRTH TRAUMA FOR BABY; INTRAVENTRICULAR HEMORRHAGE (See Guideline Notes 6,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: P10.0-P10.9,P11.0,P11.2,P11.5-P11.9,P12.2,P19.0-P19.9,P52.0-P52.1,P52.21-P52.9  
CPT: 93792,93793,96154,96155,97110-97124,97140-97168,97530,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 32**  
Condition: HEMATOLOGICAL DISORDERS OF FETUS AND NEWBORN (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: P53,P60,P61.0,P61.6  
CPT: 93792,93793,96154,96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

<b>Line:</b>	<b>33</b>
Condition:	SPINA BIFIDA (See Guideline Notes 64,65)
Treatment:	SURGICAL TREATMENT
ICD-10:	Q05.0-Q05.9,Q07.00-Q07.03
CPT:	27036,61070,61343,62160,62180-62258,63700-63710,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>34</b>
Condition:	OTHER CONGENITAL ANOMALIES OF MUSCULOSKELETAL SYSTEM (See Guideline Notes 64,65)
Treatment:	MEDICAL AND SURGICAL TREATMENT
ICD-10:	Q79.0-Q79.4,Q79.51-Q79.59
CPT:	39503,39545,49600-49611,51500,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>35</b>
Condition:	TERMINATION OF PREGNANCY (See Guideline Notes 64,65,99) (Note: This line item is not priced as part of the list)
Treatment:	INDUCED ABORTION
ICD-10:	A34,O02.89,O03.87,O04.5-O04.7,O04.80-O04.89,O07.0-O07.2,O07.30-O07.4,O08.0-O08.7,O08.81-O08.9,O35.0XX0-O35.6XX9,O35.8XX0-O35.9XX9,O36.80X0-O36.8199,Z30.8,Z33.2,Z3A.00-Z3A.22
CPT:	01966,58520,59100,59160,59200,59812,59830-59857,76801-76810,76815-76817,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S0199,S2260
<b>Line:</b>	<b>36</b>
Condition:	ACQUIRED HYPOTHYROIDISM, DYSHORMONOGENIC GOITER (See Guideline Notes 64,65)
Treatment:	MEDICAL AND SURGICAL TREATMENT
ICD-10:	E01.8,E02,E03.2-E03.9,E07.1,E89.0
CPT:	60210-60240,60270,60271,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>37</b>
Condition:	ECTOPIC PREGNANCY; HYDATIDIFORM MOLE; CHORIOCARCINOMA (See Guideline Notes 64,65,99)
Treatment:	MEDICAL AND SURGICAL TREATMENT
ICD-10:	C58,O00.00-O00.01,O00.101-O00.91,O01.0-O01.9,Z87.59
CPT:	32553,49327,49411,49412,57020,58120,58150,58180,58200,58260,58520,58541-58544,58550-58554,58570-58573,58660-58662,58673,58700-58740,58770,58940,58953,58956,59100-59151,59870,76801-76810,76815-76817,77014,77261-77290,77295,77300,77321-77370,77387,77401-77417,77424-77427,77469,77470,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>38</b>
Condition:	PRIMARY AND SECONDARY SYPHILIS (See Guideline Notes 64,65)
Treatment:	MEDICAL THERAPY
ICD-10:	A51.0-A51.2,A51.31-A51.9,A52.00-A52.09
CPT:	93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>39</b>
Condition:	DISORDERS RELATING TO LONG GESTATION AND HIGH BIRTHWEIGHT (See Guideline Notes 64,65)
Treatment:	MEDICAL THERAPY
ICD-10:	P08.0-P08.1,P08.21-P08.22
CPT:	93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

- Line: 40**  
Condition: PANHYPOPITUITARISM, IATROGENIC AND OTHER PITUITARY DISORDERS (See Guideline Notes 64,65,74)  
Treatment: MEDICAL THERAPY  
ICD-10: E23.0-E23.1,E23.6,E24.1,E89.3  
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 41**  
Condition: INTUSSUSCEPTION, VOLVULUS, INTESTINAL OBSTRUCTION, HAZARDOUS FOREIGN BODY IN GI TRACT WITH RISK OF PERFORATION OR OBSTRUCTION (See Guideline Notes 64,65,128)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: K31.5,K51.012,K51.212,K51.312,K51.412,K51.512,K51.812,K51.912,K56.1-K56.2,K56.41-K56.52,K56.600-K56.699,K59.31-K59.39,T18.2XXA-T18.2XXD,T18.3XXA-T18.3XXD,T18.4XXA-T18.4XXD,T18.5XXA-T18.5XXD,T18.8XXA-T18.8XXD,T18.9XXA-T18.9XXD,Z46.59  
CPT: 43241,43247,43500,43870,44005,44010,44020-44055,44110-44130,44139-44213,44300,44310,44320,44370,44379,44381,44384,44390,44392-44402,44404,44405,44408,44615,44625,44626,44701,45303,45307-45315,45320-45327,45332,45333,45335-45340,45346,45347,45379,45381,45384-45389,45393,45915,46604,46608,49402,49442,74283,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 42**  
Condition: CLEFT PALATE WITH AIRWAY OBSTRUCTION (See Guideline Notes 36,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT, ORTHODONTICS  
ICD-10: J39.8,J98.09,Q31.0-Q31.9,Q32.0-Q32.4,Q35.1-Q35.9  
CPT: 30140,30520,30620,31527,31545-31561,31587,31630,31631,31636-31638,31641,31780,31781,31820,33800,41510,42820-42836,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: D8010-D8040,D8070-D8694,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 43**  
Condition: NEONATAL INFECTIONS OTHER THAN SEPSIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: P38.1-P38.9,P39.0,P39.3-P39.9  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 44**  
Condition: COARCTATION OF THE AORTA (See Guideline Note 65)  
Treatment: SURGICAL TREATMENT  
ICD-10: Q25.1,Q25.29,Q25.40-Q25.42,Q25.45-Q25.46,Q25.48-Q25.49,Q25.8-Q25.9  
CPT: 33720,33722,33802,33803,33840-33853,33946-33966,33969,33984-33989,37246,37247,75557-75561,75565,92960-92971,92978-92998,93355,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 45**  
Condition: CORONARY ARTERY ANOMALY (See Guideline Note 65)  
Treatment: REIMPLANTATION OF CORONARY ARTERY  
ICD-10: Q24.5  
CPT: 33500-33510,33530,35572,92920-92938,92943,92944,92960-92998,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

- Line: 46**  
Condition: RHEUMATOID ARTHRITIS AND OTHER INFLAMMATORY POLYARTHROPATHIES (See Guideline Notes 6,64,65)  
Treatment: MEDICAL THERAPY, INJECTIONS  
ICD-10: A39.84,L40.50-L40.59,M02.011-M02.19,M02.211-M02.89,M05.00,M05.011-M05.9,M06.00,M06.011-M06.29,M06.38,M06.4,M06.80,M06.811-M06.9,M08.00,M08.011-M08.99,M14.811-M14.89  
CPT: 20550,20600-20611,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98925-98942,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 47**  
Condition: DEEP ABSCESES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS (See Guideline Notes 36,62,64,65,100)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: A06.4-A06.6,A54.82,D73.3,E32.1,G06.0-G06.2,G07-G08,H05.011-H05.049,J36,J39.0-J39.1,J85.0-J85.3,J86.0-J86.9,K35.2-K35.3,K35.80-K35.89,K36-K37,K38.0-K38.8,K50.014,K50.114,K50.814,K50.914,K51.014,K51.214,K51.314,K51.414,K51.514,K51.814,K51.914,K57.00-K57.01,K57.20-K57.21,K57.40-K57.41,K57.80-K57.81,K63.0-K63.1,K65.0-K65.1,K65.3-K65.9,K68.12-K68.19,K75.0-K75.1,M46.30-M46.39,M65.00,M65.011-M65.08,M67.20,M67.211-M67.29,M71.00,M71.011-M71.09,M71.80,M71.811-M71.89,N10,N15.1,N28.84-N28.86,N49.3,O91.111-O91.13,P78.0  
CPT: 10030,10060,10061,10160,10180,19020,20930-20938,22010,22015,22532-22632,22840-22855,22859,23031,23405,23406,23930,25000,25031,25085,25118,26020-26034,26990,27301,27603,28001,31610,31612,31613,31645,31646,32035,32036,32200-32320,32480-32488,32550,32552,32554-32562,32650-32652,32655,32656,32663-32665,32810,32815,32906,32940,33015-33050,37212,38100-38120,39000,39010,39220,42700-42725,42808-42972,43840,44120-44125,44130,44139-44160,44187-44227,44300-44316,44602-44605,44620-44626,44900-44970,45000,47010,47015,48140-48154,49020,49322,49405-49407,49422,49423,50020,50220,50391,50400,50405,50520-50526,50542-50546,50548,50575,50693-50695,50947,50948,52332,52334,61105-61253,61312-61323,61501,61514,61522,61570,61571,61582,61600,62140-62160,62163,62268,63045-63048,63075-63091,63265-63273,63295,67405,67414,67445,68400,75984,92002-92014,93792,93793,96150-96155,97605-97608,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 48**  
Condition: CHRONIC RESPIRATORY DISEASE ARISING IN THE NEONATAL PERIOD (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: P27.0-P27.9  
CPT: 31601,31820,31825,93792,93793,94774-94777,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 49**  
Condition: CONGENITAL HYDRONEPHROSIS (See Guideline Notes 64,65)  
Treatment: NEPHRECTOMY/REPAIR  
ICD-10: Q62.0,Q62.10-Q62.39  
CPT: 50100,50220-50240,50400,50405,50500,50540,50544,50546,50553,50572,50575,50600,50605,50693-50695,50722-50728,50760,50780-50785,50845-50900,50970,51535,52290-52301,52310,52334-52346,52352-52354,52356,52400,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 50**  
Condition: PULMONARY TUBERCULOSIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A15.0-A15.9,A19.0-A19.9,A31.0  
CPT: 32662,32906,32960,33015-33050,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 51**  
Condition: ACUTE PELVIC INFLAMMATORY DISEASE (See Guideline Notes 64,65,110)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: A18.17,A56.11,N70.01-N70.03,N70.91-N70.93,N71.0,N71.9,N73.0,N73.2-N73.5,N73.8-N73.9,N74  
CPT: 44960,57010,58150-58200,58260-58294,58541-58544,58550-58554,58570-58573,58660-58662,58700-58740,58820,58822,58925,58940,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

- Line: 52**  
Condition: GONOCOCCAL INFECTIONS AND OTHER SEXUALLY TRANSMITTED DISEASES OF THE ORAL, ANAL AND GENITOURINARY TRACT (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A54.00-A54.29,A54.40-A54.81,A54.83,A54.85,A54.89-A54.9,A55,A56.00-A56.8,A57-A58,A60.00-A60.9,A63.8,A64,A74.81-A74.9,N34.1  
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 53**  
Condition: PREVENTIVE DENTAL SERVICES (See Guideline Notes 17,64,65)  
Treatment: CLEANING, FLUORIDE AND SEALANTS  
ICD-10: K00.4,K08.55,Z01.20-Z01.21,Z29.3,Z91.841-Z91.849  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99188,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: D0120,D0145,D0150,D0180,D0191,D0601-D0603,D1110-D1310,D1330,D1351,D1510-D1575,D4346,D4355,D5986,D9920,G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 54**  
Condition: DENTAL CONDITIONS (E.G., INFECTION, PAIN, TRAUMA)  
Treatment: EMERGENCY DENTAL SERVICES  
ICD-10: S02.5XXA-S02.5XXB,S03.2XXA-S03.2XXD  
HCPCS: D0140,D0160,D0170,D3110,D3221,D7140,D7210,D7260-D7270,D7510,D7520,D7530,D7560,D7670,D7770,D7910,D7911,D7997,D9110,D9410,D9420,D9440,D9610,D9612,D9995,D9996
- Line: 55**  
Condition: COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS (See Coding Specification Below) (See Guideline Notes 64,65,167)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: K56.3,K80.00-K80.19,K80.21-K80.47,K80.51-K80.67,K80.71,K80.81,K81.0-K81.9,K82.0-K82.3,K82.8,K83.0-K83.3,43260-43265,43273-43278,47015,47420-47490,47533-47540,47542,47544,47554-47620,47701-47900,48548,49422,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- ICD-10 K82.8 (Other specified diseases of gallbladder) is included on Line 55 when the patient has porcelain gallbladder or gallbladder dyskinesia with a gallbladder ejection fraction <35%. Otherwise, K82.8 is included on Line 639.
- Line: 56**  
Condition: ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE (See Guideline Notes 9,64,65,77)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: I85.00-I85.11,I86.4,K22.11,K22.6,K22.8,K25.0-K25.9,K26.0-K26.9,K27.0-K27.9,K28.0-K28.9,K29.00-K29.91,K31.1,K31.3,K31.5,K31.811-K31.82,K52.0,K55.20-K55.21,K57.11,K57.31,K57.51,K57.91,K62.5,K63.81,K92.2,P54.1-P54.3,P78.82  
CPT: 37145,37160,37181-37183,37244,38100,43107-43124,43192,43201,43204,43205,43210,43227,43241,43243-43245,43255,43270,43280,43286-43288,43327,43328,43400,43401,43410,43415,43460,43501,43502,43520,43610-43641,43800,43820,43825,43840,43850,43855,43865,43870,44160,44186,44320,44391-44401,44404,44602,44603,44620-44626,45308-45320,45333-45335,45346,45381-45384,45388,46614,64680,65778-65782,68371,77014,91110,93792,93793,96150-96155,96900,96902,96910-96913,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 57**  
Condition: BURN, FULL THICKNESS GREATER THAN 10% OF BODY SURFACE (See Guideline Notes 6,64,65)  
Treatment: FREE SKIN GRAFT, MEDICAL THERAPY  
ICD-10: L00,L49.7,T20.30XA-T20.30XD,T20.311A-T20.311D,T20.312A-T20.312D,T20.319A-T20.319D,T20.32XA-T20.32XD,T20.33XA-T20.33XD,T20.34XA-T20.34XD,T20.35XA-T20.35XD,T20.36XA-T20.36XD,T20.37XA-T20.37XD,T20.39XA-T20.39XD,T20.70XA-T20.70XD,T20.711A-T20.711D,T20.712A-T20.712D,T20.719A-T20.719D,T20.72XA-T20.72XD,T20.73XA-T20.73XD,T20.74XA-T20.74XD,T20.75XA-T20.75XD,T20.76XA-T20.76XD,T20.77XA-T20.77XD,T20.79XA-T20.79XD,T21.30XA-T21.30XD,T21.31XA-T21.31XD,T21.32XA-T21.32XD,T21.33XA-T21.33XD,T21.34XA-T21.34XD,T21.35XA-T21.35XD,T21.36XA-T21.36XD,T21.37XA-T21.37XD,T21.39XA-T21.39XD,T21.70XA-T21.70XD,T21.71XA-T21.71XD,T21.72XA-T21.72XD,T21.73XA-T21.73XD,T21.74XA-T21.74XD,T21.75XA-T21.75XD,T21.76XA-T21.76XD,T21.77XA-T21.77XD,T21.79XA-T21.79XD,T22.30XA-T22.30XD,T22.311A-T22.311D,T22.312A-T22.312D,T22.319A-T22.319D,T22.321A-T22.321D,T22.322A-T22.322D,T22.329A-T22.329D,T22.331A-T22.331D,T22.332A-T22.332D,T22.339A-T22.339D,T22.341A-T22.341D,T22.342A-T22.342D,T22.349A-T22.349D,T22.351A-T22.351D,T22.352A-



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	T22.352D,T22.359A-T22.359D,T22.361A-T22.361D,T22.362A-T22.362D,T22.369A-T22.369D,T22.391A-T22.391D,T22.392A-T22.392D,T22.399A-T22.399D,T22.70XA-T22.70XD,T22.711A-T22.711D,T22.712A-T22.712D,T22.719A-T22.719D,T22.721A-T22.721D,T22.722A-T22.722D,T22.729A-T22.729D,T22.731A-T22.731D,T22.732A-T22.732D,T22.739A-T22.739D,T22.741A-T22.741D,T22.742A-T22.742D,T22.749A-T22.749D,T22.751A-T22.751D,T22.752A-T22.752D,T22.759A-T22.759D,T22.761A-T22.761D,T22.762A-T22.762D,T22.769A-T22.769D,T22.791A-T22.791D,T22.792A-T22.792D,T22.799A-T22.799D,T23.301A-T23.301D,T23.302A-T23.302D,T23.309A-T23.309D,T23.311A-T23.311D,T23.312A-T23.312D,T23.319A-T23.319D,T23.321A-T23.321D,T23.322A-T23.322D,T23.329A-T23.329D,T23.331A-T23.331D,T23.332A-T23.332D,T23.339A-T23.339D,T23.341A-T23.341D,T23.342A-T23.342D,T23.349A-T23.349D,T23.351A-T23.351D,T23.352A-T23.352D,T23.359A-T23.359D,T23.361A-T23.361D,T23.362A-T23.362D,T23.369A-T23.369D,T23.371A-T23.371D,T23.372A-T23.372D,T23.379A-T23.379D,T23.391A-T23.391D,T23.392A-T23.392D,T23.399A-T23.399D,T23.701A-T23.701D,T23.702A-T23.702D,T23.709A-T23.709D,T23.711A-T23.711D,T23.712A-T23.712D,T23.719A-T23.719D,T23.721A-T23.721D,T23.722A-T23.722D,T23.729A-T23.729D,T23.731A-T23.731D,T23.732A-T23.732D,T23.739A-T23.739D,T23.741A-T23.741D,T23.742A-T23.742D,T23.749A-T23.749D,T23.751A-T23.751D,T23.752A-T23.752D,T23.759A-T23.759D,T23.761A-T23.761D,T23.762A-T23.762D,T23.769A-T23.769D,T23.771A-T23.771D,T23.772A-T23.772D,T23.779A-T23.779D,T23.791A-T23.791D,T23.792A-T23.792D,T23.799A-T23.799D,T24.301A-T24.301D,T24.302A-T24.302D,T24.309A-T24.309D,T24.311A-T24.311D,T24.312A-T24.312D,T24.319A-T24.319D,T24.321A-T24.321D,T24.322A-T24.322D,T24.329A-T24.329D,T24.331A-T24.331D,T24.332A-T24.332D,T24.339A-T24.339D,T24.391A-T24.391D,T24.392A-T24.392D,T24.399A-T24.399D,T24.701A-T24.701D,T24.702A-T24.702D,T24.709A-T24.709D,T24.711A-T24.711D,T24.712A-T24.712D,T24.719A-T24.719D,T24.721A-T24.721D,T24.722A-T24.722D,T24.729A-T24.729D,T24.731A-T24.731D,T24.732A-T24.732D,T24.739A-T24.739D,T24.791A-T24.791D,T24.792A-T24.792D,T24.799A-T24.799D,T25.311A-T25.311D,T25.312A-T25.312D,T25.319A-T25.319D,T25.321A-T25.321D,T25.322A-T25.322D,T25.329A-T25.329D,T25.331A-T25.331D,T25.332A-T25.332D,T25.339A-T25.339D,T25.391A-T25.391D,T25.392A-T25.392D,T25.399A-T25.399D,T25.711A-T25.711D,T25.712A-T25.712D,T25.719A-T25.719D,T25.721A-T25.721D,T25.722A-T25.722D,T25.729A-T25.729D,T25.731A-T25.731D,T25.732A-T25.732D,T25.739A-T25.739D,T25.791A-T25.791D,T25.792A-T25.792D,T25.799A-T25.799D,T26.00XA-T26.00XD,T26.01XA-T26.01XD,T26.02XA-T26.02XD,T26.10XA-T26.10XD,T26.11XA-T26.11XD,T26.12XA-T26.12XD,T26.20XA-T26.20XD,T26.21XA-T26.21XD,T26.22XA-T26.22XD,T26.30XA-T26.30XD,T26.31XA-T26.31XD,T26.32XA-T26.32XD,T26.40XA-T26.40XD,T26.41XA-T26.41XD,T26.42XA-T26.42XD,T26.50XA-T26.50XD,T26.51XA-T26.51XD,T26.52XA-T26.52XD,T26.60XA-T26.60XD,T26.61XA-T26.61XD,T26.62XA-T26.62XD,T26.70XA-T26.70XD,T26.71XA-T26.71XD,T26.72XA-T26.72XD,T26.80XA-T26.80XD,T26.81XA-T26.81XD,T26.82XA-T26.82XD,T26.90XA-T26.90XD,T26.91XA-T26.91XD,T26.92XA-T26.92XD,T27.0XXA-T27.0XXD,T27.1XXA-T27.1XXD,T27.2XXA-T27.2XXD,T27.3XXA-T27.3XXD,T27.4XXA-T27.4XXD,T27.5XXA-T27.5XXD,T27.6XXA-T27.6XXD,T27.7XXA-T27.7XXD,T28.0XXA-T28.0XXD,T28.1XXA-T28.1XXD,T28.2XXA-T28.2XXD,T28.3XXA-T28.3XXD,T28.40XA-T28.40XD,T28.411A-T28.411D,T28.412A-T28.412D,T28.419A-T28.419D,T28.49XA-T28.49XD,T28.5XXA-T28.5XXD,T28.6XXA-T28.6XXD,T28.7XXA-T28.7XXD,T28.8XXA-T28.8XXD,T28.90XA-T28.90XD,T28.911A-T28.911D,T28.912A-T28.912D,T28.919A-T28.919D,T28.99XA-T28.99XD,T31.11,T31.21-T31.22,T31.31-T31.33,T31.41-T31.44,T31.51-T31.55,T31.61-T31.66,T31.71-T31.77,T31.81-T31.88,T31.91-T31.99,T32.11,T32.21-T32.22,T32.31-T32.33,T32.41-T32.44,T32.51-T32.55,T32.61-T32.66,T32.71-T32.77,T32.81-T32.88,T32.91-T32.99
CPT:	11000,11042,11045,11960-11971,15002-15005,15271-15278,16000-16036,25900-25931,26910-26952,27888,28800-28825,65778-65782,68371,92002-92014,92507,92508,92521-92524,92607-92609,92633,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9152
<b>Line:</b>	<b>58</b>
Condition:	BRONCHIECTASIS (See Guideline Notes 64,65)
Treatment:	MEDICAL AND SURGICAL TREATMENT
ICD-10:	J47.0-J47.9,J98.09
CPT:	31645,31646,32320,32480-32488,32501,32505-32507,32663,32666-32670,93792,93793,94002-94005,94640,94660-94668,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0424-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>59</b>
Condition:	END STAGE RENAL DISEASE (See Guideline Notes 7,64,65)
Treatment:	MEDICAL THERAPY INCLUDING DIALYSIS
ICD-10:	E08.21-E08.29,E09.21-E09.29,E10.21-E10.29,E11.21-E11.29,E13.21-E13.29,M32.14-M32.15,M35.04,N05.0-N05.1,N18.6
CPT:	36818-36821,36831-36838,36901-36909,49324-49326,49421,49422,49435,49436,90935-90997,93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0420,G0421,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9339,S9537



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- Line: 60**  
Condition: METABOLIC DISORDERS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: D81.810,D84.1,E71.310-E71.548,E75.00-E75.09,E75.11-E75.22,E75.240-E75.249,E75.3-E75.4,E75.6,E76.01-E76.1,E76.210-E76.9,E77.0,E77.8,E78.70,E78.9,E80.0-E80.1,E80.20-E80.3,E88.40-E88.89,H49.811-H49.819  
CPT: 93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99195,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 61**  
Condition: TORSION OF OVARY (See Guideline Notes 64,65)  
Treatment: OOPHORECTOMY, OVARIAN CYSTECTOMY  
ICD-10: N83.511-N83.53  
CPT: 58660-58662,58700-58740,58770,58925-58943,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 62**  
Condition: SUBSTANCE-INDUCED MOOD, ANXIETY, DELUSIONAL AND OBSESSIVE-COMPULSIVE DISORDERS (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F10.14,F10.150-F10.180,F10.188,F10.24,F10.250-F10.259,F10.280,F10.288,F10.94,F10.950-F10.959,F10.980,F10.988,F11.14,F11.150-F11.159,F11.188,F11.24,F11.250-F11.259,F11.288,F11.94,F11.950-F11.959,F11.988,F12.150-F12.180,F12.250-F12.280,F12.950-F12.980,F13.14,F13.150-F13.180,F13.188,F13.24,F13.250-F13.259,F13.280,F13.288,F13.94,F13.950-F13.959,F13.980,F13.988,F14.14,F14.150-F14.180,F14.188,F14.24,F14.250-F14.280,F14.288,F14.94,F14.950-F14.980,F14.988,F15.14,F15.150-F15.180,F15.188,F15.24,F15.250-F15.280,F15.288,F15.94,F15.950-F15.980,F15.988,F16.14,F16.150-F16.188,F16.24,F16.250-F16.288,F16.94,F16.950-F16.988,F18.14,F18.150-F18.159,F18.180-F18.188,F18.24,F18.250-F18.259,F18.280-F18.288,F18.94,F18.950-F18.959,F18.980-F18.988,F19.14,F19.150-F19.159,F19.180,F19.188,F19.24,F19.250-F19.259,F19.280,F19.288,F19.94,F19.950-F19.959,F19.980,F19.988  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,97810-97814,98966-98969,99051,99060,99201-99239,99281-99285,99291,99292,99324-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004-H0006,H0010,H0011,H0013-H0016,H0020,H0032-H0035,H0045,H2013,T1006,T1007
- Line: 63**  
Condition: SPONTANEOUS ABORTION; MISSED ABORTION (See Guideline Notes 64,65,99)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: O02.0-O02.1,O02.81-O02.9,O03.0-O03.2,O03.30-O03.86,O03.88-O03.9,O36.80X0-O36.80X9,Z31.82  
CPT: 58150,58152,58520,59135,59136,59200,59812-59830,59855-59857,76801-76810,76815-76817,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S0199
- Line: 64**  
Condition: CONGENITAL ANOMALIES OF UPPER ALIMENTARY TRACT, EXCLUDING TONGUE (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: Q38.4-Q38.8,Q39.0-Q39.9,Q40.0-Q40.9,Q93.81  
CPT: 31750,31760,42145,42200,42215,42815-42826,42950,43112-43124,43196,43226,43248,43249,43279,43283,43286-43288,43300-43331,43338-43361,43420,43450,43453,43496,43520,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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- Line: 65**  
Condition: SUBSTANCE-INDUCED DELIRIUM; SUBSTANCE INTOXICATION AND WITHDRAWAL  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F10.120-F10.129,F10.220-F10.239,F10.920-F10.929,F11.120-F11.129,F11.220-F11.23,F11.920-F11.93,F12.120-F12.129,F12.220-F12.229,F12.920-F12.929,F13.120-F13.129,F13.220-F13.239,F13.26-F13.27,F13.920-F13.939,F13.96-F13.97,F14.120-F14.129,F14.220-F14.23,F14.920-F14.929,F15.120-F15.129,F15.220-F15.23,F15.920-F15.93,F16.120-F16.129,F16.220-F16.229,F16.920-F16.929,F18.120-F18.129,F18.17,F18.220-F18.229,F18.27,F18.920-F18.929,F18.97,F19.120-F19.129,F19.16-F19.17,F19.220-F19.239,F19.26-F19.27,F19.920-F19.939,F19.96-F19.97  
CPT: 90785,90832-90840,93792,93793,97810-97814,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,H0010,H0011,H0013-H0015,H0032,H0033,H0035,H0038,H2013
- Line: 66**  
Condition: LARYNGEAL STENOSIS OR PARALYSIS WITH AIRWAY COMPLICATIONS (See Guideline Notes 64,65,141)  
Treatment: INCISION/EXCISION/ENDOSCOPY  
ICD-10: J38.01-J38.02,J38.6  
CPT: 31528,31529,31551-31554,31561-31571,31574,31590,31591,64905,92507,92508,92524,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 67**  
Condition: VENTRICULAR SEPTAL DEFECT (See Guideline Notes 64,65)  
Treatment: CLOSURE  
ICD-10: Q21.0,Z79.01  
CPT: 33610,33620,33621,33647,33665,33675-33688,33735-33737,33946-33966,33969,33984-33989,75557-75565,75573,92960-92971,92978-92998,93355,93581,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 68**  
Condition: ACUTE BACTERIAL MENINGITIS (See Guideline Notes 6,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A02.21,A20.3,A32.11-A32.12,A39.0,A39.3,A39.81-A39.82,G00.0-G00.9,G01-G02,G04.2  
CPT: 61000-61070,61107,61210,61215,92507,92508,92521-92526,92607-92609,92633,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9152
- Line: 69**  
Condition: ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION (See Guideline Notes 49,64,65,111)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: I20.0,I21.01-I21.A9,I22.0-I22.9,I23.1-I23.5,I23.7-I23.8,I24.0-I24.9,I25.110,I25.700,I25.710,I25.720,I25.730,I25.750,I25.760,I25.790,I51.81,R57.0,T81.11XA-T81.11XD,Z45.010-Z45.09  
CPT: 33202,33206-33210,33212-33229,33233-33238,33310,33315,33361-33430,33465,33475,33477,33500,33508-33545,33572,33681,33922,33946-33974,33984-33989,35001,35182,35189,35226,35256,35286,35572,35600,92920-92944,92960-92998,93279-93284,93286-93289,93292-93296,93355,93724,93745,93792-93798,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,K0606-K0609,S0340-S0342,S2205-S2209
- Line: 70**  
Condition: CONGENITAL PULMONARY VALVE ANOMALIES (See Guideline Notes 64,65)  
Treatment: PULMONARY VALVE REPAIR  
ICD-10: Q22.1-Q22.3,Q24.3  
CPT: 33470-33476,33478,33496,33530,33608,33620,33621,33768,33946-33966,33969,33984-33989,37246,37247,75557-75565,75573,92986-92990,93355,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



Line: 11	
Condition:	NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES (See Coding Specification Below) (See Guideline Notes 6,64,65,129,170)
Treatment:	MEDICAL AND SURGICAL TREATMENT (E.G., G-TUBES, J-TUBES, RESPIRATORS, TRACHEOSTOMY, UROLOGICAL PROCEDURES)
ICD-10:	A33.A50.40,A50.43,A50.45,A52.10-A52.15,A52.17-A52.19,A52.3,A81.00-A81.83,A87.1-A87.2,A88.8,A89,C70.0-C70.9,C71.0-C71.9,C72.0-C72.1,C72.20-C72.9,D33.9,D81.3,D81.5,E00.0-E00.9,E45,E70.20-E70.29,E70.330-E70.331,E70.8-E70.9,E71.0,E71.110-E71.548,E72.00-E72.51,E72.59-E72.9,E74.00-E74.09,E75.00-E75.09,E75.11-E75.23,E75.240-E75.6,E76.01-E76.1,E76.210-E76.9,E77.0-E77.9,E78.70-E78.9,E79.1-E79.9,E80.0-E80.1,E80.20-E80.3,E83.00-E83.09,E88.2,E88.40-E88.49,E88.89,F01.50-F01.51,F03.90-F03.91,F06.1,F06.8,F07.89,F71-F79,F84.0-F84.3,F84.8,G04.1,G04.81-G04.91,G10,G11.0-G11.4,G12.0-G12.1,G12.21-G12.9,G13.1-G13.8,G14-G20,G21.0,G21.11-G21.9,G23.0-G23.9,G25.82,G25.9,G30.0-G30.8,G31.01-G31.83,G31.85-G31.9,G32.0,G32.81-G32.89,G35,G36.0-G36.9,G37.0-G37.9,G40.011-G40.019,G40.111-G40.119,G40.211-G40.219,G40.311-G40.319,G40.411-G40.419,G40.811,G40.89,G40.911-G40.919,G60.0-G60.1,G60.3-G60.8,G61.0-G61.1,G61.81-G61.89,G62.0-G62.2,G62.81-G62.89,G64,G71.0,G71.11-G71.8,G72.0-G72.3,G72.41-G72.89,G73.7,G80.0-G80.9,G81.00-G81.94,G82.20-G82.54,G83.0,G83.30-G83.9,G90.01-G90.1,G90.3-G90.4,G91.0-G91.9,G92,G93.0-G93.1,G93.40-G93.81,G93.89,G94,G95.0,G95.11-G95.89,G97.0,G97.2,G97.31-G97.32,G97.48-G97.49,G97.61-G97.82,G98.0,G99.0-G99.8,H49.811-H49.819,I61.0-I61.9,I62.00-I62.9,I63.30,I63.311-I63.312,I63.319-I63.322,I63.329-I63.332,I63.339-I63.342,I63.349-I63.412,I63.419-I63.422,I63.429-I63.432,I63.439-I63.442,I63.449-I63.512,I63.519-I63.522,I63.529-I63.532,I63.539-I63.542,I64.49-I63.9,I67.3,I67.81-I67.83,I67.841-I67.89,I69.010-I69.018,I69.020-I69.022,I69.051-I69.069,I69.091-I69.092,I69.110-I69.118,I69.121-I69.122,I69.128,I69.151-I69.169,I69.191-I69.192,I69.210-I69.218,I69.221-I69.222,I69.251-I69.269,I69.291-I69.292,I69.310-I69.318,I69.321-I69.322,I69.351-I69.369,I69.391-I69.392,I69.810-I69.818,I69.822,I69.851-I69.869,I69.891-I69.892,I69.910-I69.918,I69.922,I69.951-I69.969,I69.991-I69.992,I97.810-I97.822,K59.2,M62.3,M62.58-M62.59,M62.89,N31.0-N31.9,P07.00-P07.39,P10.0-P10.9,P11.0,P11.2,P11.5-P11.9,P19.0-P19.9,P24.00-P24.21,P24.80-P24.9,P35.0-P35.9,P37.0-P37.9,P39.2,P50.0-P50.9,P51.0-P51.9,P52.0-P52.1,P52.21-P52.9,P54.1-P54.9,P55.1-P55.9,P56.0,P56.90-P56.99,P57.0,P91.2,P91.60-P91.63,P96.81,Q00.0-Q00.2,Q01.0-Q01.9,Q02,Q03.0-Q03.9,Q04.0-Q04.9,Q05.0-Q05.9,Q06.0-Q06.9,Q07.00-Q07.9,Q74.3,Q77.3,Q77.6,Q78.0-Q78.3,Q78.5-Q78.6,Q85.1,Q86.0-Q86.8,Q87.1-Q87.3,Q87.40,Q87.410-Q87.89,Q89.4-Q89.8,Q90.0-Q90.9,Q91.0-Q91.7,Q92.0-Q92.5,Q92.62-Q92.9,Q93.0-Q93.7,Q93.81-Q93.9,Q95.2-Q95.8,Q96.0-Q96.9,Q97.0-Q97.8,Q98.0-Q98.3,Q98.5-Q98.8,Q99.0-Q99.8,R13.0,R13.10-R13.19,R15.0,R15.2-R15.9,R41.4,R41.81,R53.2,R54,S06.370A-S06.370D,S06.810A-S06.810D,S06.811A-S06.811D,S06.812A-S06.812D,S06.813A-S06.813D,S06.814A-S06.814D,S06.815A-S06.815D,S06.816A-S06.816D,S06.817A-S06.817D,S06.819D,S06.820A-S06.820D,S06.821A-S06.821D,S06.822A-S06.822D,S06.823A-S06.823D,S06.824A-S06.824D,S06.825A-S06.825D,S06.826A-S06.826D,S06.827A-S06.827D,S06.829D,S06.890A-S06.890D,S06.891A-S06.891D,S06.892A-S06.892D,S06.893A-S06.893D,S06.894A-S06.894D,S06.895A-S06.895D,S06.896A-S06.896D,S06.897A-S06.897D,S06.899D,S06.9X0A-S06.9X0D,S06.9X1A-S06.9X1D,S06.9X2A-S06.9X2D,S06.9X3A-S06.9X3D,S06.9X4A-S06.9X4D,S06.9X5A-S06.9X5D,S06.9X6A-S06.9X6D,S06.9X7A-S06.9X7D,S14.0XXA-S14.0XXD,S14.101A-S14.101D,S14.102A-S14.102D,S14.103A-S14.103D,S14.104A-S14.104D,S14.105A-S14.105D,S14.106A-S14.106D,S14.107A-S14.107D,S14.108A-S14.108D,S14.109A-S14.109D,S14.111A-S14.111D,S14.112A-S14.112D,S14.113A-S14.113D,S14.114A-S14.114D,S14.115A-S14.115D,S14.116A-S14.116D,S14.117A-S14.117D,S14.118A-S14.118D,S14.119A-S14.119D,S14.121A-S14.121D,S14.122A-S14.122D,S14.123A-S14.123D,S14.124A-S14.124D,S14.125A-S14.125D,S14.126A-S14.126D,S14.127A-S14.127D,S14.128A-S14.128D,S14.129A-S14.129D,S14.131A-S14.131D,S14.132A-S14.132D,S14.133A-S14.133D,S14.134A-S14.134D,S14.135A-S14.135D,S14.136A-S14.136D,S14.137A-S14.137D,S14.138A-S14.138D,S14.139A-S14.139D,S14.141A-S14.141D,S14.142A-S14.142D,S14.143A-S14.143D,S14.144A-S14.144D,S14.145A-S14.145D,S14.146A-S14.146D,S14.147A-S14.147D,S14.148A-S14.148D,S14.149A-S14.149D,S14.151A-S14.151D,S14.152A-S14.152D,S14.153A-S14.153D,S14.154A-S14.154D,S14.155A-S14.155D,S14.156A-S14.156D,S14.157A-S14.157D,S14.158A-S14.158D,S14.159A-S14.159D,S14.2XXA-S14.2XXD,S14.3XXA-S14.3XXD,S24.0XXA-S24.0XXD,S24.101A-S24.101D,S24.102A-S24.102D,S24.103A-S24.103D,S24.104A-S24.104D,S24.109A-S24.109D,S24.111A-S24.111D,S24.112A-S24.112D,S24.113A-S24.113D,S24.114A-S24.114D,S24.119A-S24.119D,S24.131A-S24.131D,S24.132A-S24.132D,S24.133A-S24.133D,S24.134A-S24.134



PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

T71.141D,T71.143A-T71.143D,T71.144A-T71.144D,T71.151A-T71.151D,T71.152A-T71.152D,T71.153A-T71.153D,T71.154A-T71.154D,T71.161A-T71.161D,T71.162A-T71.162D,T71.163A-T71.163D,T71.164A-T71.164D,T71.191A-T71.191D,T71.192A-T71.192D,T71.193A-T71.193D,T71.194A-T71.194D,T71.20XA-T71.20XD,T71.21XA-T71.21XD,T71.221A-T71.221D,T71.222A-T71.222D,T71.223A-T71.223D,T71.224A-T71.224D,T71.231A-T71.231D,T71.232A-T71.232D,T71.233A-T71.233D,T71.234A-T71.234D,T71.29XA-T71.29XD,T71.9XXA-T71.9XXD,T74.4XXA-T74.4XXD,T75.01XA-T75.01XD,T75.09XA-T75.09XD,T75.1XXA-T75.1XXD,T75.4XXA-T75.4XXD,T78.00XA-T78.00XD,T78.01XA-T78.01XD,T78.02XA-T78.02XD,T78.03XA-T78.03XD,T78.04XA-T78.04XD,T78.05XA-T78.05XD,T78.06XA-T78.06XD,T78.07XA-T78.07XD,T78.08XA-T78.08XD,T78.09XA-T78.09XD,T78.3XXA-T78.3XXD,T78.8XXA-T78.8XXD,T79.0XXA-T79.0XXD,T79.4XXA-T79.4XXD,T79.6XXA-T79.6XXD,T88.2XXA-T88.2XXD,T88.51XA-T88.51XD,T88.6XXA-T88.6XXD,Z43.0-Z43.4,Z43.8,Z45.49,Z46.59

CPT: 15845,31600,31601,31610-31614,31630,31631,31636-31638,31641,31730-31760,31820-31830,43810-43825,44130,44139-44160,44186-44188,44204-44213,44300-44320,44620-44626,44701,46750-46754,49442,51040,51102,51700,51705,51710,51880,51960,52277,53431-53442,53445,61215,62320-62323,62350-62362,62367-62370,77387,77401-77432,77469,77470,92526,93792,93793,94002-94005,94640,94660-94668,95990,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: D5937,D5992,D5993,G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

CPT codes 62320-3 are only included on Lines 71 and 292 for trials of antispasmodics in preparation for placement of a baclofen pump.

**Line: 72**  
**Condition:** BURN, PARTIAL THICKNESS GREATER THAN 30% OF BODY SURFACE OR WITH VITAL SITE; FULL THICKNESS, LESS THAN 10% OF BODY SURFACE (See Guideline Notes 6,64,65)  
**Treatment:** FREE SKIN GRAFT, MEDICAL THERAPY  
**ICD-10:** L00,L49.7,T20.20XA-T20.20XD,T20.211A-T20.211D,T20.212A-T20.212D,T20.219A-T20.219D,T20.22XA-T20.22XD,T20.23XA-T20.23XD,T20.24XA-T20.24XD,T20.25XA-T20.25XD,T20.26XA-T20.26XD,T20.27XA-T20.27XD,T20.29XA-T20.29XD,T20.30XA-T20.30XD,T20.311A-T20.311D,T20.312A-T20.312D,T20.319A-T20.319D,T20.32XA-T20.32XD,T20.33XA-T20.33XD,T20.34XA-T20.34XD,T20.37XA-T20.37XD,T20.39XA-T20.39XD,T20.60XA-T20.60XD,T20.611A-T20.611D,T20.612A-T20.612D,T20.619A-T20.619D,T20.62XA-T20.62XD,T20.63XA-T20.63XD,T20.64XA-T20.64XD,T20.65XA-T20.65XD,T20.66XA-T20.66XD,T20.67XA-T20.67XD,T20.69XA-T20.69XD,T20.70XA-T20.70XD,T20.711A-T20.711D,T20.712A-T20.712D,T20.719A-T20.719D,T20.72XA-T20.72XD,T20.73XA-T20.73XD,T20.74XA-T20.74XD,T20.77XA-T20.77XD,T20.79XA-T20.79XD,T21.20XA-T21.20XD,T21.21XA-T21.21XD,T21.22XA-T21.22XD,T21.23XA-T21.23XD,T21.24XA-T21.24XD,T21.25XA-T21.25XD,T21.26XA-T21.26XD,T21.27XA-T21.27XD,T21.29XA-T21.29XD,T21.36XA-T21.36XD,T21.37XA-T21.37XD,T21.60XA-T21.60XD,T21.61XA-T21.61XD,T21.62XA-T21.62XD,T21.63XA-T21.63XD,T21.64XA-T21.64XD,T21.65XA-T21.65XD,T21.66XA-T21.66XD,T21.67XA-T21.67XD,T21.69XA-T21.69XD,T21.76XA-T21.76XD,T21.77XA-T21.77XD,T22.20XA-T22.20XD,T22.211A-T22.211D,T22.212A-T22.212D,T22.219A-T22.219D,T22.221A-T22.221D,T22.222A-T22.222D,T22.229A-T22.229D,T22.231A-T22.231D,T22.232A-T22.232D,T22.239A-T22.239D,T22.241A-T22.241D,T22.242A-T22.242D,T22.249A-T22.249D,T22.251A-T22.251D,T22.252A-T22.252D,T22.259A-T22.259D,T22.261A-T22.261D,T22.262A-T22.262D,T22.269A-T22.269D,T22.291A-T22.291D,T22.292A-T22.292D,T22.299A-T22.299D,T22.60XA-T22.60XD,T22.611A-T22.611D,T22.612A-T22.612D,T22.619A-T22.619D,T22.621A-T22.621D,T22.622A-T22.622D,T22.629A-T22.629D,T22.631A-T22.631D,T22.632A-T22.632D,T22.639A-T22.639D,T22.641A-T22.641D,T22.642A-T22.642D,T22.649A-T22.649D,T22.651A-T22.651D,T22.652A-T22.652D,T22.659A-T22.659D,T22.661A-T22.661D,T22.662A-T22.662D,T22.669A-T22.669D,T22.691A-T22.691D,T22.692A-T22.692D,T22.699A-T22.699D,T23.201A-T23.201D,T23.202A-T23.202D,T23.209A-T23.209D,T23.211A-T23.211D,T23.212A-T23.212D,T23.219A-T23.219D,T23.221A-T23.221D,T23.222A-T23.222D,T23.229A-T23.229D,T23.231A-T23.231D,T23.232A-T23.232D,T23.239A-T23.239D,T23.241A-T23.241D,T23.242A-T23.242D,T23.249A-T23.249D,T23.251A-T23.251D,T23.252A-T23.252D,T23.259A-T23.259D,T23.261A-T23.261D,T23.262A-T23.262D,T23.269A-T23.269D,T23.271A-T23.271D,T23.272A-T23.272D,T23.279A-T23.279D,T23.291A-T23.291D,T23.292A-T23.292D,T23.299A-T23.299D,T23.351A-T23.351D,T23.352A-T23.352D,T23.359A-T23.359D,T23.601A-T23.601D,T23.602A-T23.602D,T23.609A-T23.609D,T23.611A-T23.611D,T23.612A-T23.612D,T23.619A-T23.619D,T23.621A-T23.621D,T23.622A-T23.622D,T23.629A-T23.629D,T23.631A-T23.631D,T23.632A-T23.632D,T23.639A-T23.639D,T23.641A-T23.641D,T23.642A-T23.642D,T23.649A-T23.649D,T23.651A-T23.651D,T23.652A-T23.652D,T23.659A-T23.659D,T23.661A-T23.661D,T23.662A-T23.662D,T23.669A-T23.669D,T23.671A-T23.671D,T23.672A-T23.672D,T23.679A-T23.679D,T23.691A-T23.691D,T23.692A-T23.692D,T23.699A-T23.699D,T23.751A-T23.751D,T23.752A-T23.752D,T23.759A-T23.759D,T24.201A-T24.201D,T24.202A-T24.202D,T24.209A-T24.209D,T24.211A-T24.211D,T24.212A-T24.212D,T24.219A-T24.219D,T24.221A-T24.221D,T24.222A-T24.222D,T24.229A-T24.229D,T24.231A-T24.231D,T24.232A-T24.232D,T24.239A-T24.239D,T24.291A-T24.291D,T24.292A-T24.292D,T24.299A-T24.299D,T24.601A-T24.601D,T24.602A-T24.602D,T24.609A-T24.609D,T24.611A-T24.611D,T24.612A-T24.612D,T24.619A-T24.619D,T24.621A-T24.621D,T24.622A-T24.622D,T24.629A-T24.629D,T24.631A-T24.631D,T24.632A-T24.632D,T24.639A-T24.639D,T24.691A-T24.691D,T24.692A-T24.692D,T24.699A-T24.699D,T25.211A-T25.211D,T25.212A-T25.212D,T25.219A-T25.219D,T25.221A-T25.221D,T25.222A-T25.222D,T25.229A-T25.229D,T25.231A-T25.231D,T25.232A-T25.232D,T25.239A-T25.239D,T25.291A-T25.291D,T25.292A-T25.292D,T25.299A-T25.299D,T25.321A-T25.321D,T25.322A-T25.322D,T25.329A-T25.329D,T25.611A-T25.611D,T25.612A-T25.612D,T25.619A-T25.619D,T25.621A-T25.621D,T25.622A-T25.622D,T25.629A-T25.629D,T25.631A-T25.631D,T25.632A-T25.632D,T25.639A-T25.639D,T25.691A-T25.691D,T25.692A-T25.692D,T25.699A-T25.699D,T25.721A-T25.721D,T25.722A-T25.722D



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T25.722D,T25.729A-T25.729D,T31.0,T31.10,T31.20,T31.30,T31.40,T31.50,T31.60,T31.70,T31.80,T31.90,T32.0,  
T32.10,T32.20,T32.30,T32.40,T32.50,T32.60,T32.70,T32.80,T32.90  
CPT: 11000,11042,11045,11960-11971,15002-15005,15271-15278,16020-16036,92507,92508,92521-92524,92607-  
92609,92633,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,  
98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-  
99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,  
G0513,G0514,S9152

**Line: 73**  
Condition: POLYCYTHEMIA NEONATORUM, SYMPTOMATIC (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: P61.1  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-  
99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 74**  
Condition: DERMATOMYOSITIS, POLYMYOSITIS (See Guideline Notes 6,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: M33.00-M33.99,M35.8,M36.0  
CPT: 90284,93792,93793,96150-96155,97110,97116,97161-97168,98966-98969,99051,99060,99070,99078,99184,  
99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 75**  
Condition: ADDISON'S DISEASE (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: E27.1-E27.3,E27.40-E27.49,E31.0,E31.8-E31.9,E89.6  
CPT: 92081-92083,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-  
99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 76**  
Condition: HYPERTENSION AND HYPERTENSIVE DISEASE (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: I10,I11.0-I11.9,I15.2-I15.9,I16.0-I16.9,I67.4  
CPT: 92960-92971,92978-92998,93792-93798,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,  
99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-  
99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,  
G0508-G0511,G0513,G0514

**Line: 77**  
Condition: PATENT DUCTUS ARTERIOSUS; AORTIC PULMONARY FISTULA/WINDOW (See Guideline Notes 64,65)  
Treatment: LIGATION  
ICD-10: P29.30-P29.38,Q21.4,Q25.0  
CPT: 33500-33504,33702,33710,33813-33824,33946-33966,33969,33984-33989,92960-92971,92978-92998,93355,  
93582,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,  
99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,  
G0508-G0511,G0513,G0514

**Line: 78**  
Condition: INJURY TO MAJOR BLOOD VESSELS  
Treatment: LIGATION/REPAIR  
ICD-10: S09.0XXA-S09.0XXD,S15.001A-S15.001D,S15.002A-S15.002D,S15.009A-S15.009D,S15.011A-S15.011D,  
S15.012A-S15.012D,S15.019A-S15.019D,S15.021A-S15.021D,S15.022A-S15.022D,S15.029A-S15.029D,  
S15.091A-S15.091D,S15.092A-S15.092D,S15.099A-S15.099D,S15.101A-S15.101D,S15.102A-S15.102D,  
S15.109A-S15.109D,S15.111A-S15.111D,S15.112A-S15.112D,S15.119A-S15.119D,S15.121A-S15.121D,  
S15.122A-S15.122D,S15.129A-S15.129D,S15.191A-S15.191D,S15.192A-S15.192D,S15.199A-S15.199D,  
S15.201A-S15.201D,S15.202A-S15.202D,S15.209A-S15.209D,S15.211A-S15.211D,S15.212A-S15.212D,  
S15.219A-S15.219D,S15.221A-S15.221D,S15.222A-S15.222D,S15.229A-S15.229D,S15.291A-S15.291D,  
S15.292A-S15.292D,S15.299A-S15.299D,S15.301A-S15.301D,S15.302A-S15.302D,S15.309A-S15.309D,  
S15.311A-S15.311D,S15.312A-S15.312D,S15.319A-S15.319D,S15.321A-S15.321D,S15.322A-S15.322D,  
S15.329A-S15.329D,S15.391A-S15.391D,S15.392A-S15.392D,S15.399A-S15.399D,S15.8XXA-S15.8XXD,  
S15.9XXA-S15.9XXD,S25.00XA-S25.00XD,S25.01XA-S25.01XD,S25.02XA-S25.02XD,S25.09XA-S25.09XD,  
S25.101A-S25.101D,S25.102A-S25.102D,S25.109A-S25.109D,S25.111A-S25.111D,S25.112A-S25.112D,



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S25.119A-S25.119D,S25.121A-S25.121D,S25.122A-S25.122D,S25.129A-S25.129D,S25.191A-S25.191D,  
S25.192A-S25.192D,S25.199A-S25.199D,S25.20XA-S25.20XD,S25.21XA-S25.21XD,S25.22XA-S25.22XD,  
S25.29XA-S25.29XD,S25.301A-S25.301D,S25.302A-S25.302D,S25.309A-S25.309D,S25.311A-S25.311D,  
S25.312A-S25.312D,S25.319A-S25.319D,S25.321A-S25.321D,S25.322A-S25.322D,S25.329A-S25.329D,  
S25.391A-S25.391D,S25.392A-S25.392D,S25.399A-S25.399D,S25.401A-S25.401D,S25.402A-S25.402D,  
S25.409A-S25.409D,S25.411A-S25.411D,S25.412A-S25.412D,S25.419A-S25.419D,S25.421A-S25.421D,  
S25.422A-S25.422D,S25.429A-S25.429D,S25.491A-S25.491D,S25.492A-S25.492D,S25.499A-S25.499D,  
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S25.519A-S25.519D,S25.591A-S25.591D,S25.592A-S25.592D,S25.599A-S25.599D,S25.801A-S25.801D,  
S25.802A-S25.802D,S25.809A-S25.809D,S25.811A-S25.811D,S25.812A-S25.812D,S25.819A-S25.819D,  
S25.891A-S25.891D,S25.892A-S25.892D,S25.899A-S25.899D,S25.90XA-S25.90XD,S25.91XA-S25.91XD,  
S25.99XA-S25.99XD,S35.00XA-S35.00XD,S35.01XA-S35.01XD,S35.02XA-S35.02XD,S35.09XA-S35.09XD,  
S35.10XA-S35.10XD,S35.11XA-S35.11XD,S35.12XA-S35.12XD,S35.19XA-S35.19XD,S35.211A-S35.211D,  
S35.212A-S35.212D,S35.218A-S35.218D,S35.219A-S35.219D,S35.221A-S35.221D,S35.222A-S35.222D,  
S35.228A-S35.228D,S35.229A-S35.229D,S35.231A-S35.231D,S35.232A-S35.232D,S35.238A-S35.238D,  
S35.239A-S35.239D,S35.291A-S35.291D,S35.292A-S35.292D,S35.298A-S35.298D,S35.299A-S35.299D,  
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S55.109A-S55.109D,S55.111A-S55.111D,S55.112A-S55.112D,S55.119A-S55.119D,S55.191A-S55.191D,  
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S55.812A-S55.812D,S55.819A-S55.819D,S55.891A-S55.891D,S55.892A-S55.892D,S55.899A-S55.899D,  
S55.901A-S55.901D,S55.902A-S55.902D,S55.909A-S55.909D,S55.911A-S55.911D,S55.912A-S55.912D,  
S55.919A-S55.919D,S55.991A-S55.991D,S55.992A-S55.992D,S55.999A-S55.999D,S65.001A-S65.001D,  
S65.002A-S65.002D,S65.009A-S65.009D,S65.011A-S65.011D,S65.012A-S65.012D,S65.019A-S65.019D,  
S65.091A-S65.091D,S65.092A-S65.092D,S65.099A-S65.099D,S65.101A-S65.101D,S65.102A-S65.102D,  
S65.109A-S65.109D,S65.111A-S65.111D,S65.112A-S65.112D,S65.119A-S65.119D,S65.191A-S65.191D,  
S65.192A-S65.192D,S65.199A-S65.199D,S65.201A-S65.201D,S65.202A-S65.202D,S65.209A-S65.209D,  
S65.211A-S65.211D,S65.212A-S65.212D,S65.219A-S65.219D,S65.291A-S65.291D,S65.292A-S65.292D,  
S65.299A-S65.299D,S65.301A-S65.301D,S65.302A-S65.302D,S65.309A-S65.309D,S65.311A-S65.311D,  
S65.312A-S65.312D,S65.319A-S65.319D,S65.391A-S65.391D,S65.392A-S65.392D,S65.399A-S65.399D,  
S65.801A-S65.801D,S65.802A-S65.802D,S65.809A-S65.809D,S65.811A-S65.811D,S65.812A-S65.812D,  
S65.819A-S65.819D,S65.891A-S65.891D,S65.892A-S65.892D,S65.899A-S65.899D,S65.901A-S65.901D,  
S65.902A-S65.902D,S65.909A-S65.909D,S65.911A-S65.911D,S65.912A-S65.912D,S65.919A-S65.919D,  
S65.991A-S65.991D,S65.992A-S65.992D,S65.999A-S65.999D,S75.001A-S75.001D,S75.002A-S75.002D,  
S75.009A-S75.009D,S75.011A-S75.011D,S75.012A-S75.012D,S75.019A-S75.019D,S75.021A-S75.021D,  
S75.022A-S75.022D,S75.029A-S75.029D,S75.091A-S75.091D,S75.092A-S75.092D,S75.099A-S75.099D,  
S75.101A-S75.101D,S75.102A-S75.102D,S75.109A-S75.109D,S75.111A-S75.111D,S75.112A-S75.112D,  
S75.119A-S75.119D,S75.121A-S75.121D,S75.122A-S75.122D,S75.129A-S75.129D,S75.191A-S75.191D,  
S75.192A-S75.192D,S75.199A-S75.199D,S75.201A-S75.201D,S75.202A-S75.202D,S75.209A-S75.209D,  
S75.211A-S75.211D,S75.212A-S75.212D,S75.219A-S75.219D,S75.221A-S75.221D,S75.222A-S75.222D,  
S75.229A-S75.229D,S75.291A-S75.291D,S75.292A-S75.292D,S75.299A-S75.299D,S75.801A-S75.801D,  
S75.802A-S75.802D,S75.809A-S75.809D,S75.811A-S75.811D,S75.812A-S75.812D,S75.819A-S75.819D,  
S75.891A-S75.891D,S75.892A-S75.892D,S75.899A-S75.899D,S75.901A-S75.901D,S75.902A-S75.902D,  
S75.909A-S75.909D,S75.911A-S75.911D,S75.912A-S75.912D,S75.919A-S75.919D,S75.991A-S75.991D,  
S75.992A-S75.992D,S75.999A-S75.999D,S85.001A-S85.001D,S85.002A-S85.002D,S85.009A-S85.009D,  
S85.011A-S85.011D,S85.012A-S85.012D,S85.019A-S85.019D,S85.091A-S85.091D,S85.092A-S85.092D,  
S85.099A-S85.099D,S85.101A-S85.101D,S85.102A-S85.102D,S85.109A-S85.109D,S85.111A-S85.111D,  
S85.112A-S85.112D,S85.119A-S85.119D,S85.121A-S85.121D,S85.122A-S85.122D,S85.129A-S85.129D,  
S85.131A-S85.131D,S85.132A-S85.132D,S85.139A-S85.139D,S85.141A-S85.141D,S85.142A-S85.142D,  
S85.149A-S85.149D,S85.151A-S85.151D,S85.152A-S85.152D,S85.159A-S85.159D,S85.161A-S85.161D,  
S85.162A-S85.162D,S85.169A-S85.169D,S85.171A-S85.171D,S85.172A-S85.172D,S85.179A-S85.179D,  
S85.181A-S85.181D,S85.182A-S85.182D,S85.189A-S85.189D,S85.201A-S85.201D,S85.202A-S85.202D,



PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

S85.209A-S85.209D,S85.211A-S85.211D,S85.212A-S85.212D,S85.219A-S85.219D,S85.291A-S85.291D,  
S85.292A-S85.292D,S85.299A-S85.299D,S85.301A-S85.301D,S85.302A-S85.302D,S85.309A-S85.309D,  
S85.311A-S85.311D,S85.312A-S85.312D,S85.319A-S85.319D,S85.391A-S85.391D,S85.392A-S85.392D,  
S85.399A-S85.399D,S85.401A-S85.401D,S85.402A-S85.402D,S85.409A-S85.409D,S85.411A-S85.411D,  
S85.412A-S85.412D,S85.419A-S85.419D,S85.491A-S85.491D,S85.492A-S85.492D,S85.499A-S85.499D,  
S85.501A-S85.501D,S85.502A-S85.502D,S85.509A-S85.509D,S85.511A-S85.511D,S85.512A-S85.512D,  
S85.519A-S85.519D,S85.591A-S85.591D,S85.592A-S85.592D,S85.599A-S85.599D,S85.801A-S85.801D,  
S85.802A-S85.802D,S85.809A-S85.809D,S85.811A-S85.811D,S85.812A-S85.812D,S85.819A-S85.819D,  
S85.891A-S85.891D,S85.892A-S85.892D,S85.899A-S85.899D,S85.901A-S85.901D,S85.902A-S85.902D,  
S85.909A-S85.909D,S85.911A-S85.911D,S85.912A-S85.912D,S85.919A-S85.919D,S85.991A-S85.991D,  
S85.992A-S85.992D,S85.999A-S85.999D  
CPT: 32654,33320-33335,33880-33891,34502,34839-34848,35189-35206,35211,35216,35226-35246,35256-35276,  
35286,35500,35506,35516,35616,37565,37615,37616,37618,37650,92960-92971,92986-92998,93792-93798,  
98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-  
99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,  
G0508-G0511,G0513,G0514

**Line: 79**  
Condition: PHLEBITIS AND THROMBOPHLEBITIS, DEEP (See Guideline Notes 64,65,147)  
Treatment: MEDICAL THERAPY  
ICD-10: I80.10-I80.13,I80.201-I80.299,I82.401-I82.5Z9,Z79.01  
CPT: 11042,11045,32661,35700,35860,35875,35876,35903,37187-37193,37212-37214,37248,37249,37500,37650,  
37660,37735-37761,37785,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-  
99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 80**  
Condition: INJURY TO INTERNAL ORGANS (See Guideline Notes 62,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: B51.0,S21.301A-S21.301D,S21.302A-S21.302D,S21.309A-S21.309D,S21.311A-S21.311D,S21.312A-S21.312D,  
S21.319A-S21.319D,S21.321A-S21.321D,S21.322A-S21.322D,S21.329A-S21.329D,S21.331A-S21.331D,  
S21.332A-S21.332D,S21.339A-S21.339D,S21.341A-S21.341D,S21.342A-S21.342D,S21.349A-S21.349D,  
S21.351A-S21.351D,S21.352A-S21.352D,S21.359A-S21.359D,S21.401A-S21.401D,S21.402A-S21.402D,  
S21.409A-S21.409D,S21.411A-S21.411D,S21.412A-S21.412D,S21.419A-S21.419D,S21.421A-S21.421D,  
S21.422A-S21.422D,S21.429A-S21.429D,S21.431A-S21.431D,S21.432A-S21.432D,S21.439A-S21.439D,  
S21.441A-S21.441D,S21.442A-S21.442D,S21.449A-S21.449D,S21.451A-S21.451D,S21.452A-S21.452D,  
S21.459A-S21.459D,S26.00XA-S26.00XD,S26.01XA-S26.01XD,S26.020A-S26.020D,S26.021A-S26.021D,  
S26.022A-S26.022D,S26.09XA-S26.09XD,S26.10XA-S26.10XD,S26.11XA-S26.11XD,S26.12XA-S26.12XD,  
S26.19XA-S26.19XD,S26.90XA-S26.90XD,S26.91XA-S26.91XD,S26.92XA-S26.92XD,S26.99XA-S26.99XD,  
S27.301A-S27.301D,S27.302A-S27.302D,S27.309A-S27.309D,S27.311A-S27.311D,S27.312A-S27.312D,  
S27.319A-S27.319D,S27.321A-S27.321D,S27.322A-S27.322D,S27.329A-S27.329D,S27.331A-S27.331D,  
S27.332A-S27.332D,S27.339A-S27.339D,S27.391A-S27.391D,S27.392A-S27.392D,S27.399A-S27.399D,  
S27.401A-S27.401D,S27.402A-S27.402D,S27.409A-S27.409D,S27.411A-S27.411D,S27.412A-S27.412D,  
S27.419A-S27.419D,S27.421A-S27.421D,S27.422A-S27.422D,S27.429A-S27.429D,S27.431A-S27.431D,  
S27.432A-S27.432D,S27.439A-S27.439D,S27.491A-S27.491D,S27.492A-S27.492D,S27.499A-S27.499D,  
S27.50XA-S27.50XD,S27.51XA-S27.51XD,S27.52XA-S27.52XD,S27.53XA-S27.53XD,S27.59XA-S27.59XD,  
S27.60XA-S27.60XD,S27.63XA-S27.63XD,S27.69XA-S27.69XD,S27.802A-S27.802D,S27.803A-S27.803D,  
S27.808A-S27.808D,S27.809A-S27.809D,S27.892A-S27.892D,S27.893A-S27.893D,S27.898A-S27.898D,  
S27.899A-S27.899D,S27.9XXA-S27.9XXD,S31.001A-S31.001D,S31.011A-S31.011D,S31.021A-S31.021D,  
S31.031A-S31.031D,S31.041A-S31.041D,S31.051A-S31.051D,S31.600A-S31.600D,S31.601A-S31.601D,  
S31.602A-S31.602D,S31.603A-S31.603D,S31.604A-S31.604D,S31.605A-S31.605D,S31.609A-S31.609D,  
S31.610A-S31.610D,S31.611A-S31.611D,S31.612A-S31.612D,S31.613A-S31.613D,S31.614A-S31.614D,  
S31.615A-S31.615D,S31.619A-S31.619D,S31.620A-S31.620D,S31.621A-S31.621D,S31.622A-S31.622D,  
S31.623A-S31.623D,S31.624A-S31.624D,S31.625A-S31.625D,S31.629A-S31.629D,S31.630A-S31.630D,  
S31.631A-S31.631D,S31.632A-S31.632D,S31.633A-S31.633D,S31.634A-S31.634D,S31.635A-S31.635D,  
S31.639A-S31.639D,S31.640A-S31.640D,S31.641A-S31.641D,S31.642A-S31.642D,S31.643A-S31.643D,  
S31.644A-S31.644D,S31.645A-S31.645D,S31.649A-S31.649D,S31.650A-S31.650D,S31.651A-S31.651D,  
S31.652A-S31.652D,S31.653A-S31.653D,S31.654A-S31.654D,S31.655A-S31.655D,S31.659A-S31.659D,  
S36.00XA-S36.00XD,S36.020A-S36.020D,S36.021A-S36.021D,S36.029A-S36.029D,S36.030A-S36.030D,  
S36.031A-S36.031D,S36.032A-S36.032D,S36.039A-S36.039D,S36.09XA-S36.09XD,S36.112A-S36.112D,  
S36.113A-S36.113D,S36.114A-S36.114D,S36.115A-S36.115D,S36.116A-S36.116D,S36.118A-S36.118D,  
S36.119A-S36.119D,S36.122A-S36.122D,S36.123A-S36.123D,S36.128A-S36.128D,S36.129A-S36.129D,  
S36.13XA-S36.13XD,S36.200A-S36.200D,S36.201A-S36.201D,S36.202A-S36.202D,S36.209A-S36.209D,  
S36.220A-S36.220D,S36.221A-S36.221D,S36.222A-S36.222D,S36.229A-S36.229D,S36.230A-S36.230D,  
S36.231A-S36.231D,S36.232A-S36.232D,S36.239A-S36.239D,S36.240A-S36.240D,S36.241A-S36.241D,  
S36.242A-S36.242D,S36.249A-S36.249D,S36.250A-S36.250D,S36.251A-S36.251D,S36.252A-S36.252D,  
S36.259A-S36.259D,S36.260A-S36.260D,S36.261A-S36.261D,S36.262A-S36.262D,S36.269A-S36.269D,  
S36.290A-S36.290D,S36.291A-S36.291D,S36.292A-S36.292D,S36.299A-S36.299D,S36.30XA-S36.30XD,  
S36.32XA-S36.32XD,S36.33XA-S36.33XD,S36.39XA-S36.39XD,S36.400A-S36.400D,S36.408A-S36.408D,  
S36.409A-S36.409D,S36.410A-S36.410D,S36.418A-S36.418D,S36.419A-S36.419D,S36.420A-S36.420D,



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S36.428A-S36.428D,S36.429A-S36.429D,S36.430A-S36.430D,S36.438A-S36.438D,S36.439A-S36.439D,  
S36.490A-S36.490D,S36.498A-S36.498D,S36.499A-S36.499D,S36.500A-S36.500D,S36.501A-S36.501D,  
S36.502A-S36.502D,S36.503A-S36.503D,S36.508A-S36.508D,S36.509A-S36.509D,S36.510A-S36.510D,  
S36.511A-S36.511D,S36.512A-S36.512D,S36.513A-S36.513D,S36.518A-S36.518D,S36.519A-S36.519D,  
S36.520A-S36.520D,S36.521A-S36.521D,S36.522A-S36.522D,S36.523A-S36.523D,S36.528A-S36.528D,  
S36.529A-S36.529D,S36.530A-S36.530D,S36.531A-S36.531D,S36.532A-S36.532D,S36.533A-S36.533D,  
S36.538A-S36.538D,S36.539A-S36.539D,S36.590A-S36.590D,S36.591A-S36.591D,S36.592A-S36.592D,  
S36.593A-S36.593D,S36.598A-S36.598D,S36.599A-S36.599D,S36.60XA-S36.60XD,S36.61XA-S36.61XD,  
S36.62XA-S36.62XD,S36.63XA-S36.63XD,S36.69XA-S36.69XD,S36.81XA-S36.81XD,S36.892A-S36.892D,  
S36.893A-S36.893D,S36.898A-S36.898D,S36.899A-S36.899D,S36.90XA-S36.90XD,S36.92XA-S36.92XD,  
S36.93XA-S36.93XD,S36.99XA-S36.99XD,S37.001A-S37.001D,S37.002A-S37.002D,S37.009A-S37.009D,  
S37.011A-S37.011D,S37.012A-S37.012D,S37.019A-S37.019D,S37.021A-S37.021D,S37.022A-S37.022D,  
S37.029A-S37.029D,S37.031A-S37.031D,S37.032A-S37.032D,S37.039A-S37.039D,S37.041A-S37.041D,  
S37.042A-S37.042D,S37.049A-S37.049D,S37.051A-S37.051D,S37.052A-S37.052D,S37.059A-S37.059D,  
S37.061A-S37.061D,S37.062A-S37.062D,S37.069A-S37.069D,S37.091A-S37.091D,S37.092A-S37.092D,  
S37.099A-S37.099D,S37.10XA-S37.10XD,S37.12XA-S37.12XD,S37.13XA-S37.13XD,S37.19XA-S37.19XD,  
S37.20XA-S37.20XD,S37.22XA-S37.22XD,S37.23XA-S37.23XD,S37.29XA-S37.29XD,S37.30XA-S37.30XD,  
S37.32XA-S37.32XD,S37.33XA-S37.33XD,S37.39XA-S37.39XD,S37.401A-S37.401D,S37.402A-S37.402D,  
S37.409A-S37.409D,S37.421A-S37.421D,S37.422A-S37.422D,S37.429A-S37.429D,S37.431A-S37.431D,  
S37.432A-S37.432D,S37.439A-S37.439D,S37.491A-S37.491D,S37.492A-S37.492D,S37.499A-S37.499D,  
S37.501A-S37.501D,S37.502A-S37.502D,S37.509A-S37.509D,S37.511A-S37.511D,S37.512A-S37.512D,  
S37.519A-S37.519D,S37.521A-S37.521D,S37.522A-S37.522D,S37.529A-S37.529D,S37.531A-S37.531D,  
S37.532A-S37.532D,S37.539A-S37.539D,S37.591A-S37.591D,S37.592A-S37.592D,S37.599A-S37.599D,  
S37.60XA-S37.60XD,S37.62XA-S37.62XD,S37.63XA-S37.63XD,S37.69XA-S37.69XD,S37.812A-S37.812D,  
S37.813A-S37.813D,S37.818A-S37.818D,S37.819A-S37.819D,S37.822A-S37.822D,S37.823A-S37.823D,  
S37.828A-S37.828D,S37.829A-S37.829D,S37.892A-S37.892D,S37.893A-S37.893D,S37.898A-S37.898D,  
S37.899A-S37.899D,S37.90XA-S37.90XD,S37.92XA-S37.92XD,S37.93XA-S37.93XD,S37.99XA-S37.99XD,  
T79.4XXA-T79.4XXD,T79.7XXA-T79.7XXD  
CPT: 31775,31805,32110-32124,32653,32654,32658,32820,33300-33335,34839-34848,37619,39501,39540,39545,  
43840,44120-44125,44139-44160,44227,44320,44602-44605,44620-44626,44701,45562,45563,47120-47130,  
47350-47362,47533-47537,47802,47900,48545,50220,50546,50693-50695,50740-50760,50947,50948,51102,  
51860,51865,52310,52315,52332,53502-53515,58520,93792,93793,97605-97608,98966-98969,99051,99060,  
99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-  
99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 81**  
Condition: FRACTURE OF HIP (See Guideline Notes 6,15,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: M84.359A-M84.359G,M84.459A-M84.459G,M84.559A-M84.559G,M84.659A-M84.659G,M91.10-M91.92,  
S72.001A-S72.001J,S72.002A-S72.002J,S72.009A-S72.009J,S72.011A-S72.011J,S72.012A-S72.012J,  
S72.019A-S72.019J,S72.021A-S72.021J,S72.022A-S72.022J,S72.023A-S72.023J,S72.024A-S72.024J,  
S72.025A-S72.025J,S72.026A-S72.026J,S72.031A-S72.031J,S72.032A-S72.032J,S72.033A-S72.033J,  
S72.034A-S72.034J,S72.035A-S72.035J,S72.036A-S72.036J,S72.041A-S72.041J,S72.042A-S72.042J,  
S72.043A-S72.043J,S72.044A-S72.044J,S72.045A-S72.045J,S72.046A-S72.046J,S72.051A-S72.051J,  
S72.052A-S72.052J,S72.059A-S72.059J,S72.061A-S72.061J,S72.062A-S72.062J,S72.063A-S72.063J,  
S72.064A-S72.064J,S72.065A-S72.065J,S72.066A-S72.066J,S72.091A-S72.091J,S72.092A-S72.092J,  
S72.099A-S72.099J,S72.101A-S72.101J,S72.102A-S72.102J,S72.109A-S72.109J,S72.111A-S72.111J,  
S72.112A-S72.112J,S72.113A-S72.113J,S72.114A-S72.114J,S72.115A-S72.115J,S72.116A-S72.116J,  
S72.121A-S72.121J,S72.122A-S72.122J,S72.123A-S72.123J,S72.124A-S72.124J,S72.125A-S72.125J,  
S72.126A-S72.126J,S72.131A-S72.131J,S72.132A-S72.132J,S72.133A-S72.133J,S72.134A-S72.134J,  
S72.135A-S72.135J,S72.136A-S72.136J,S72.141A-S72.141J,S72.142A-S72.142J,S72.143A-S72.143J,  
S72.144A-S72.144J,S72.145A-S72.145J,S72.146A-S72.146J,S72.21XA-S72.21XJ,S72.22XA-S72.22XJ,  
S72.23XA-S72.23XJ,S72.24XA-S72.24XJ,S72.25XA-S72.25XJ,S72.26XA-S72.26XJ,S79.001A-S79.001G,  
S79.002A-S79.002G,S79.009A-S79.009G,S79.011A-S79.011G,S79.012A-S79.012G,S79.019A-S79.019G,  
S79.091A-S79.091G,S79.092A-S79.092G,S79.099A-S79.099G,Z47.1-Z47.2  
CPT: 20680,27125-27132,27230-27248,27254,27267-27269,27506,27656,29035-29046,29305,29325,29700,29710,  
29720,77014,77261-77290,77295,77300,77331-77336,77387,77401-77417,77427,77470,93792,93793,97012,  
97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,  
99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,  
G0508-G0511,G0513,G0514



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- Line: 82**  
Condition: MYOCARDITIS, PERICARDITIS, AND ENDOCARDITIS (See Guideline Notes 18,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: A18.84,A32.82,A39.50-A39.53,A52.03,A52.06,B26.82,B37.6,B57.0,D86.85,I09.0,I09.2,I23.0,I30.0-I30.9,I31.0-I31.9,I32,I33.0-I33.9,I39,I40.0-I40.9,I41,I51.4,I97.0,M32.11-M32.12,Z45.09  
CPT: 31750,31760,32659,32661,33010-33050,33361-33391,33405-33413,33418,33419,33425-33465,33475,33477,33530,33946-33966,33969,33975-33993,35820,92960-92971,92978-92998,93355,93750,93792-93798,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9348
- Line: 83**  
Condition: DEEP OPEN WOUND OF NECK, INCLUDING LARYNX; FRACTURE OF LARYNX OR TRACHEA (See Guideline Notes 64,65)  
Treatment: REPAIR  
ICD-10: S11.011A-S11.011D,S11.012A-S11.012D,S11.013A-S11.013D,S11.014A-S11.014D,S11.015A-S11.015D,S11.019A-S11.019D,S11.021A-S11.021D,S11.022A-S11.022D,S11.023A-S11.023D,S11.024A-S11.024D,S11.025A-S11.025D,S11.029A-S11.029D,S11.031A-S11.031D,S11.032A-S11.032D,S11.033A-S11.033D,S11.034A-S11.034D,S11.035A-S11.035D,S11.039A-S11.039D,S11.10XA-S11.10XD,S11.11XA-S11.11XD,S11.12XA-S11.12XD,S11.13XA-S11.13XD,S11.14XA-S11.14XD,S11.15XA-S11.15XD,S11.20XA-S11.20XD,S11.21XA-S11.21XD,S11.22XA-S11.22XD,S11.23XA-S11.23XD,S11.24XA-S11.24XD,S11.25XA-S11.25XD,S11.80XA-S11.80XD,S11.81XA-S11.81XD,S11.82XA-S11.82XD,S11.83XA-S11.83XD,S11.84XA-S11.84XD,S11.85XA-S11.85XD,S11.89XA-S11.89XD,S11.90XA-S11.90XD,S11.91XA-S11.91XD,S11.92XA-S11.92XD,S11.93XA-S11.93XD,S11.94XA-S11.94XD,S11.95XA-S11.95XD,S12.8XXA-S12.8XXD,S13.20XA-S13.20XD,S13.29XA-S13.29XD,S16.2XXA-S16.2XXD  
CPT: 11010-11012,12001-12007,13131-13133,15004,15005,20100,31528,31529,31584,31630,31766,31780,31781,31800,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 84**  
Condition: DIABETES MELLITUS WITH END STAGE RENAL DISEASE (See Coding Specification Below)  
Treatment: SIMULTANEOUS PANCREAS/KIDNEY (SPK) TRANSPLANT, PANCREAS AFTER KIDNEY (PAK) TRANSPLANT  
ICD-10: E10.21-E10.29,T86.10-T86.19,T86.850-T86.899,Z48.22,Z48.288  
CPT: 48160,48550-48556,50300-50365,76776,86825-86835,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S2065
- SPK included for type I diabetes mellitus with end stage renal disease (E10.2), PAK only included for other type I diabetes mellitus with secondary diagnosis of Z94.0.
- Line: 85**  
Condition: ENDOCARDIAL CUSHION DEFECTS (See Guideline Notes 64,65)  
Treatment: REPAIR  
ICD-10: Q20.6-Q20.8,Q21.2,Q21.8-Q21.9  
CPT: 33620,33621,33645-33670,33946-33966,33969,33984-33989,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,96154,96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 86**  
Condition: CONGENITAL PULMONARY VALVE ATRESIA (See Guideline Notes 64,65)  
Treatment: SHUNT/REPAIR  
ICD-10: Q22.0  
CPT: 33470-33474,33530,33608,33620,33621,33750-33766,33920,33925,33926,33946-33966,33969,33984-33989,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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- Line: 87**  
Condition: CONGENITAL ANOMALIES OF GENITOURINARY SYSTEM (See Guideline Notes 64,65,72)  
Treatment: RECONSTRUCTION  
ICD-10: Q55.23,Q55.3,Q60.3,Q61.00-Q61.9,Q62.4-Q62.5,Q62.60-Q62.69,Q62.8,Q63.0-Q63.9,Q64.10,Q64.12-Q64.6,Q64.71,Q64.73-Q64.74,Q64.79  
CPT: 15002-15005,45820,50040,50045,50100,50125,50135,50220-50290,50390,50400,50405,50540,50542-50546,50548,50553,50572,50605,50650,50722-50728,50760,50780-50785,50825-50860,50947,50948,50970,51020-51045,51080-51597,51715,51800-51980,52214,52290,52300,53020,53025,53080,53085,53210,53215,53400-53460,53621,55175,55180,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 88**  
Condition: NECROTIZING ENTEROCOLITIS IN FETUS OR NEWBORN (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: K55.30-K55.33,P77.1-P77.9,Z46.59  
CPT: 44120-44125,44130,44139-44160,44300-44320,44340-44346,44602-44605,44620-44650,49442,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 89**  
Condition: DISCORDANT CARDIOVASCULAR CONNECTIONS (See Guideline Notes 64,65)  
Treatment: REPAIR  
ICD-10: Q20.1-Q20.3,Q20.5,Q20.8-Q20.9,Q93.81  
CPT: 33418,33419,33611,33612,33620,33621,33684,33735-33766,33770-33783,33946-33966,33969,33984-33989,42225,42226,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 90**  
Condition: CONGENITAL MITRAL VALVE STENOSIS/INSUFFICIENCY (See Guideline Notes 64,65)  
Treatment: MITRAL VALVE REPAIR/REPLACEMENT  
ICD-10: Q23.2-Q23.3,Z79.01  
CPT: 33418-33430,33496,33620,33621,33946-33966,33969,33984-33989,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 91**  
Condition: GUILLAIN-BARRE SYNDROME (See Guideline Notes 6,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: G61.0  
CPT: 31600,31610,36514,36516,90284,92507,92508,92521-92526,92607-92609,92633,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9152
- Line: 92**  
Condition: SEVERE/MODERATE HEAD INJURY: HEMATOMA/EDEMA WITH PERSISTENT SYMPTOMS (See Guideline Notes 6,64,65,90,121)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: S02.0XXA-S02.0XXG,S02.101A-S02.101G,S02.102A-S02.102G,S02.109A-S02.109G,S02.110A-S02.110G,S02.111A-S02.111G,S02.112A-S02.112G,S02.113A-S02.113G,S02.118A-S02.118G,S02.119A-S02.119G,S02.11AA-S02.11AG,S02.11BA-S02.11BG,S02.11CA-S02.11CG,S02.11DA-S02.11DG,S02.11EA-S02.11EG,S02.11FA-S02.11FG,S02.11GA-S02.11GG,S02.11HA-S02.11HG,S02.19XB-S02.19XG,S02.80XA-S02.80XG,S02.81XA-S02.81XG,S02.82XA-S02.82XG,S02.91XA-S02.91XG,S04.041A-S04.041D,S04.042A-S04.042D,S04.049A-S04.049D,S06.0X0A-S06.0X0D,S06.0X1A-S06.0X1D,S06.0X9A-S06.0X9D,S06.1X7A-S06.1X8A,S06.2X0A-S06.2X0D,S06.2X1A-S06.2X1D,S06.2X2A-S06.2X2D,S06.2X3A-S06.2X3D,S06.2X4A-S06.2X4D,S06.2X5A-S06.2X5D,S06.2X6A-S06.2X6D,S06.2X7A-S06.2X9D,S06.300A-S06.300D,S06.301A-S06.301D,S06.302A-S06.302D,S06.303A-S06.303D,S06.304A-S06.304D,S06.305A-S06.305D,S06.306A-S06.306D,S06.307A-S06.309D,S06.310A-S06.310D,S06.311A-S06.311D,S06.312A-S06.312D,S06.313A-S06.313D,S06.314A-S06.314D,S06.315A-S06.315D,S06.316A-S06.316D,S06.317A-S06.319D,S06.320A-S06.320D,S06.321A-S06.321D,S06.322A-S06.322D,S06.323A-S06.323D,S06.324A-S06.324D,S06.325A-S06.325D,



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S06.326A-S06.326D,S06.327A-S06.329D,S06.330A-S06.330D,S06.331A-S06.331D,S06.332A-S06.332D,  
S06.333A-S06.333D,S06.334A-S06.334D,S06.335A-S06.335D,S06.336A-S06.336D,S06.337A-S06.339D,  
S06.5X8A,S06.6X7A-S06.6X8A  
CPT: 11010-11012,11971,21100,21110,61107,61108,61210,61312-61322,61340,61345,61571,62000-62010,62140-  
62148,92507,92508,92521-92526,92607-92609,92633,93792,93793,96118,96150-96155,97012,97110-97127,  
97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,  
99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,  
G0513-G0515,S9152

**Line: 93**  
Condition: CHILDHOOD LEUKEMIAS (See Guideline Notes 7,11,12,16,64,65)  
Treatment: MEDICAL THERAPY, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C90.10-C90.12,C91.00-C91.02,C92.00-C92.02,C93.30-C93.32,C95.00-C95.02,D46.20-D46.22,D61.810,G89.3,  
Z45.49,Z51.0,Z51.12  
CPT: 32553,49411,77014,77261-77295,77300-77307,77321-77370,77385-77387,77401-77427,77469,77520-77525,  
81246,93792,93793,95990,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-  
98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,  
99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,  
G6001-G6017,S9537

**Line: 94**  
Condition: UNDESCENDED TESTICLE (See Guideline Note 72)  
Treatment: SURGICAL TREATMENT  
ICD-10: Q53.00-Q53.10,Q53.111-Q53.9,Q55.22  
CPT: 54512-54522,54550,54560,54620-54660,54690,54692,55200,93792,93793,98966-98969,99051,99060,99070,  
99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,  
99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 95**  
Condition: HEREDITARY IMMUNE DEFICIENCIES (See Guideline Notes 7,11,14)  
Treatment: BONE MARROW TRANSPLANT  
ICD-10: D61.810,D81.0-D81.4,D81.6-D81.7,D81.89-D81.9,D82.0-D82.1,T86.01-T86.09,Z48.290,Z52.000-Z52.098,Z52.3  
CPT: 36680,38204-38215,38240,38242,38243,86825-86835,90284,93792,93793,96150-96155,96377,96405,96406,  
96420-96440,96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,  
99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,  
S2142,S2150,S9537

**Line: 96**  
Condition: DIABETIC AND OTHER RETINOPATHY (See Guideline Notes 64,65,116)  
Treatment: MEDICAL, SURGICAL, AND LASER TREATMENT  
ICD-10: D18.09,E08.311-E08.319,E08.3211-E08.3599,E08.37X1-E08.39,E09.311-E09.319,E09.3211-E09.3599,  
E09.37X1-E09.39,E10.311-E10.319,E10.3211-E10.3599,E10.37X1-E10.39,E11.311-E11.319,E11.3211-E11.3599,  
E11.37X1-E11.39,E13.311-E13.319,E13.3211-E13.3599,E13.37X1-E13.39,H31.401-H31.8,H35.021-H35.09,  
H35.20-H35.23,H35.60-H35.63  
CPT: 67027,67028,67036-67043,67208,67210,67220,67227-67229,67515,92002-92014,92018-92060,92081-92136,  
92225-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-  
99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 97**  
Condition: BORDERLINE PERSONALITY DISORDER (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F60.3  
CPT: 90785,90832-90840,90846,90847,90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,  
99324-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,  
G0508-G0511,G0513,G0514,H0004,H0018,H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-  
H2023,H2027,H2032,H2033,S5151,S9125,S9480,S9484,T1005



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<b>Line:</b>	<b>98</b>
Condition:	HEART FAILURE (See Guideline Notes 18,64,65)
Treatment:	MEDICAL THERAPY
ICD-10:	I09.81,I27.0-I27.1,I27.20-I27.81,I27.83-I27.9,I50.1,I50.20-I50.43,I50.810-I50.9,I97.110-I97.111,I97.130-I97.191,J81.0-J81.1,P29.0,Z45.09,Z79.01
CPT:	33946-33993,92920-92938,92943,92944,92960-92998,93355,93750,93792-93798,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9348
<b>Line:</b>	<b>99</b>
Condition:	CARDIOMYOPATHY (See Guideline Notes 49,64,65,124)
Treatment:	MEDICAL AND SURGICAL TREATMENT
ICD-10:	B57.2,I42.0-I42.9,I43,I51.5,Z45.010-Z45.09,Z79.01
CPT:	21630,33010,33215,33216,33218,33220,33223-33226,33230,33231,33240-33249,33262-33264,33270-33273,33414-33416,33508-33530,92960-92971,92978-92998,93282-93284,93287,93289,93292,93295,93296,93583,93644,93724,93745,93792-93798,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0448,G0463-G0467,G0490,G0508-G0511,G0513,G0514,K0606-K0609,S0340-S0342,S9348
<b>Line:</b>	<b>100</b>
Condition:	END STAGE RENAL DISEASE
Treatment:	RENAL TRANSPLANT
ICD-10:	D30.9,D57.1,D59.3,D69.0,E08.21-E08.29,E09.21-E09.29,E10.21-E10.29,E11.21-E11.29,E13.21-E13.29,E75.21-E75.22,E75.240-E75.249,E75.3,E77.0,E77.8,E78.71-E78.72,I12.0,M30.0-M30.2,M30.8,M31.0,M31.31,M31.7,M32.14-M32.19,M35.04,N00.8,N01.0-N01.9,N02.0-N02.9,N03.0-N03.9,N04.0-N04.9,N05.0-N05.9,N06.0-N06.9,N07.0-N07.9,N08,N11.0-N11.8,N14.0-N14.4,N15.0,N15.8-N15.9,N16,N17.0-N17.9,N18.5-N18.6,N26.1,N26.9,N28.0,Q60.0-Q60.2,Q60.4-Q60.6,Q61.19-Q61.5,Q62.0,Q62.10-Q62.39,Q79.4,Q79.51,Q87.2-Q87.3,Q87.5,Q87.81,Q87.89,Q89.8,T86.10-T86.19,Z48.22,Z52.4
CPT:	36825,36830,50300-50370,50547,52310,76776,86825-86835,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>101</b>
Condition:	CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION (See Guideline Notes 64,65)
Treatment:	MEDICAL AND SURGICAL TREATMENT
ICD-10:	K31.6,P76.0-P76.9,P78.1,P78.81,P78.84-P78.89,Q40.0,Q41.0-Q41.9,Q42.0-Q42.9,Q43.0-Q43.9,Q45.0-Q45.9,T86.890-T86.899,Z46.59
CPT:	31750,31760,32905,32906,39503,39545,43500-43520,43620-43640,43800-43825,43840,43850,43860,43870,43880,44005,44010,44020,44021,44050,44055,44110-44130,44139-44227,44300-44346,44363-44370,44378,44379,44381,44384,44391-44402,44404,44405,44408-44701,44715-44721,44800-44955,45000-45020,45108-45123,45130-45150,45303,45308-45320,45327,45333-45335,45338,45340,45346,45347,45381-45389,45393-45397,45800,45905,45910,46040,46045,46060-46080,46270,46275,46604,46610-46614,46705-46754,47300,47533-47540,47542,47544,47554-47556,47600-47620,47701,47715-47999,48120-48146,48150,48500-48556,49203-49250,49324,49325,49421-49423,49442,49600-49611,49904,49905,51500,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>102</b>
Condition:	HEMOLYTIC DISEASE DUE TO ISOIMMUNIZATION, ANEMIA DUE TO TRANSPLACENTAL HEMORRHAGE, AND FETAL AND NEONATAL JAUNDICE (See Guideline Notes 64,65)
Treatment:	MEDICAL THERAPY
ICD-10:	E80.5,P50.0-P50.9,P51.0-P51.9,P55.0-P55.9,P57.0-P57.9,P58.0-P58.3,P58.41-P58.9,P59.0-P59.1,P59.20-P59.9,P61.3-P61.4
CPT:	93792,93793,96900,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>103</b>
Condition:	POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS (See Guideline Notes 64,65,156)
Treatment:	MEDICAL THERAPY
ICD-10:	E67.0,E67.3,P93.0-P93.8,T36.0X1A-T36.0X1D,T36.0X2A-T36.0X2D,T36.0X3A-T36.0X3D,T36.0X4A-T36.0X4D,T36.0X5A-T36.0X5D,T36.1X1A-T36.1X1D,T36.1X2A-T36.1X2D,T36.1X3A-T36.1X3D,T36.1X4A-T36.1X4D,T36.1X5A-T36.1X5D,T36.2X1A-T36.2X1D,T36.2X2A-T36.2X2D,T36.2X3A-T36.2X3D,T36.2X4A-T36.2X4D,



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T36.2X5A-T36.2X5D,T36.3X1A-T36.3X1D,T36.3X2A-T36.3X2D,T36.3X3A-T36.3X3D,T36.3X4A-T36.3X4D,  
T36.3X5A-T36.3X5D,T36.4X1A-T36.4X1D,T36.4X2A-T36.4X2D,T36.4X3A-T36.4X3D,T36.4X4A-T36.4X4D,  
T36.4X5A-T36.4X5D,T36.5X1A-T36.5X1D,T36.5X2A-T36.5X2D,T36.5X3A-T36.5X3D,T36.5X4A-T36.5X4D,  
T36.5X5A-T36.5X5D,T36.6X1A-T36.6X1D,T36.6X2A-T36.6X2D,T36.6X3A-T36.6X3D,T36.6X4A-T36.6X4D,  
T36.6X5A-T36.6X5D,T36.7X1A-T36.7X1D,T36.7X2A-T36.7X2D,T36.7X3A-T36.7X3D,T36.7X4A-T36.7X4D,  
T36.7X5A-T36.7X5D,T36.8X1A-T36.8X1D,T36.8X2A-T36.8X2D,T36.8X3A-T36.8X3D,T36.8X4A-T36.8X4D,  
T36.8X5A-T36.8X5D,T36.91XA-T36.91XD,T36.92XA-T36.92XD,T36.93XA-T36.93XD,T36.94XA-T36.94XD,  
T36.95XA-T36.95XD,T37.0X1A-T37.0X1D,T37.0X2A-T37.0X2D,T37.0X3A-T37.0X3D,T37.0X4A-T37.0X4D,  
T37.0X5A-T37.0X5D,T37.1X1A-T37.1X1D,T37.1X2A-T37.1X2D,T37.1X3A-T37.1X3D,T37.1X4A-T37.1X4D,  
T37.1X5A-T37.1X5D,T37.2X1A-T37.2X1D,T37.2X2A-T37.2X2D,T37.2X3A-T37.2X3D,T37.2X4A-T37.2X4D,  
T37.2X5A-T37.2X5D,T37.3X1A-T37.3X1D,T37.3X2A-T37.3X2D,T37.3X3A-T37.3X3D,T37.3X4A-T37.3X4D,  
T37.3X5A-T37.3X5D,T37.4X1A-T37.4X1D,T37.4X2A-T37.4X2D,T37.4X3A-T37.4X3D,T37.4X4A-T37.4X4D,  
T37.4X5A-T37.4X5D,T37.5X1A-T37.5X1D,T37.5X2A-T37.5X2D,T37.5X3A-T37.5X3D,T37.5X4A-T37.5X4D,  
T37.5X5A-T37.5X5D,T37.8X1A-T37.8X1D,T37.8X2A-T37.8X2D,T37.8X3A-T37.8X3D,T37.8X4A-T37.8X4D,  
T37.8X5A-T37.8X5D,T37.91XA-T37.91XD,T37.92XA-T37.92XD,T37.93XA-T37.93XD,T37.94XA-T37.94XD,  
T37.95XA-T37.95XD,T38.0X1A-T38.0X1D,T38.0X2A-T38.0X2D,T38.0X3A-T38.0X3D,T38.0X4A-T38.0X4D,  
T38.0X5A-T38.0X5D,T38.1X1A-T38.1X1D,T38.1X2A-T38.1X2D,T38.1X3A-T38.1X3D,T38.1X4A-T38.1X4D,  
T38.1X5A-T38.1X5D,T38.1X6A-T38.1X6D,T38.2X1A-T38.2X1D,T38.2X2A-T38.2X2D,T38.2X3A-T38.2X3D,  
T38.2X4A-T38.2X4D,T38.2X5A-T38.2X5D,T38.2X6A-T38.2X6D,T38.3X1A-T38.3X1D,T38.3X2A-T38.3X2D,  
T38.3X3A-T38.3X3D,T38.3X4A-T38.3X4D,T38.3X5A-T38.3X5D,T38.4X1A-T38.4X1D,T38.4X2A-T38.4X2D,  
T38.4X3A-T38.4X3D,T38.4X4A-T38.4X4D,T38.4X5A-T38.4X5D,T38.5X1A-T38.5X1D,T38.5X2A-T38.5X2D,  
T38.5X3A-T38.5X3D,T38.5X4A-T38.5X4D,T38.5X5A-T38.5X5D,T38.6X1A-T38.6X1D,T38.6X2A-T38.6X2D,  
T38.6X3A-T38.6X3D,T38.6X4A-T38.6X4D,T38.6X5A-T38.6X5D,T38.7X1A-T38.7X1D,T38.7X2A-T38.7X2D,  
T38.7X3A-T38.7X3D,T38.7X4A-T38.7X4D,T38.7X5A-T38.7X5D,T38.801A-T38.801D,T38.802A-T38.802D,  
T38.803A-T38.803D,T38.804A-T38.804D,T38.805A-T38.805D,T38.811A-T38.811D,T38.812A-T38.812D,  
T38.813A-T38.813D,T38.814A-T38.814D,T38.815A-T38.815D,T38.891A-T38.891D,T38.892A-T38.892D,  
T38.893A-T38.893D,T38.894A-T38.894D,T38.895A-T38.895D,T38.901A-T38.901D,T38.902A-T38.902D,  
T38.903A-T38.903D,T38.904A-T38.904D,T38.905A-T38.905D,T38.991A-T38.991D,T38.992A-T38.992D,  
T38.993A-T38.993D,T38.994A-T38.994D,T38.995A-T38.995D,T39.011A-T39.011D,T39.012A-T39.012D,  
T39.013A-T39.013D,T39.014A-T39.014D,T39.015A-T39.015D,T39.091A-T39.091D,T39.092A-T39.092D,  
T39.093A-T39.093D,T39.094A-T39.094D,T39.095A-T39.095D,T39.1X1A-T39.1X1D,T39.1X2A-T39.1X2D,  
T39.1X3A-T39.1X3D,T39.1X4A-T39.1X4D,T39.1X5A-T39.1X5D,T39.2X1A-T39.2X1D,T39.2X2A-T39.2X2D,  
T39.2X3A-T39.2X3D,T39.2X4A-T39.2X4D,T39.2X5A-T39.2X5D,T39.311A-T39.311D,T39.312A-T39.312D,  
T39.313A-T39.313D,T39.314A-T39.314D,T39.315A-T39.315D,T39.391A-T39.391D,T39.392A-T39.392D,  
T39.393A-T39.393D,T39.394A-T39.394D,T39.395A-T39.395D,T39.4X1A-T39.4X1D,T39.4X2A-T39.4X2D,  
T39.4X3A-T39.4X3D,T39.4X4A-T39.4X4D,T39.4X5A-T39.4X5D,T39.8X1A-T39.8X1D,T39.8X2A-T39.8X2D,  
T39.8X3A-T39.8X3D,T39.8X4A-T39.8X4D,T39.8X5A-T39.8X5D,T39.91XA-T39.91XD,T39.92XA-T39.92XD,  
T39.93XA-T39.93XD,T39.94XA-T39.94XD,T39.95XA-T39.95XD,T40.0X1A-T40.0X1D,T40.0X2A-T40.0X2D,  
T40.0X3A-T40.0X3D,T40.0X4A-T40.0X4D,T40.0X5A-T40.0X5D,T40.1X1A-T40.1X1D,T40.1X2A-T40.1X2D,  
T40.1X3A-T40.1X3D,T40.1X4A-T40.1X4D,T40.2X1A-T40.2X1D,T40.2X2A-T40.2X2D,T40.2X3A-T40.2X3D,  
T40.2X4A-T40.2X4D,T40.2X5A-T40.2X5D,T40.3X1A-T40.3X1D,T40.3X2A-T40.3X2D,T40.3X3A-T40.3X3D,  
T40.3X4A-T40.3X4D,T40.3X5A-T40.3X5D,T40.4X1A-T40.4X1D,T40.4X2A-T40.4X2D,T40.4X3A-T40.4X3D,  
T40.4X4A-T40.4X4D,T40.4X5A-T40.4X5D,T40.5X1A-T40.5X1D,T40.5X2A-T40.5X2D,T40.5X3A-T40.5X3D,  
T40.5X4A-T40.5X4D,T40.5X5A-T40.5X5D,T40.601A-T40.601D,T40.602A-T40.602D,T40.603A-T40.603D,  
T40.604A-T40.604D,T40.605A-T40.605D,T40.691A-T40.691D,T40.692A-T40.692D,T40.693A-T40.693D,  
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T40.7X4A-T40.7X4D,T40.7X5A-T40.7X5D,T40.8X1A-T40.8X1D,T40.8X2A-T40.8X2D,T40.8X3A-T40.8X3D,  
T40.8X4A-T40.8X4D,T40.901A-T40.901D,T40.902A-T40.902D,T40.903A-T40.903D,T40.904A-T40.904D,  
T40.905A-T40.905D,T40.991A-T40.991D,T40.992A-T40.992D,T40.993A-T40.993D,T40.994A-T40.994D,  
T40.995A-T40.995D,T41.0X1A-T41.0X1D,T41.0X2A-T41.0X2D,T41.0X3A-T41.0X3D,T41.0X4A-T41.0X4D,  
T41.0X5A-T41.0X5D,T41.1X1A-T41.1X1D,T41.1X2A-T41.1X2D,T41.1X3A-T41.1X3D,T41.1X4A-T41.1X4D,  
T41.1X5A-T41.1X5D,T41.201A-T41.201D,T41.202A-T41.202D,T41.203A-T41.203D,T41.204A-T41.204D,  
T41.205A-T41.205D,T41.291A-T41.291D,T41.292A-T41.292D,T41.293A-T41.293D,T41.294A-T41.294D,  
T41.295A-T41.295D,T41.3X1A-T41.3X1D,T41.3X2A-T41.3X2D,T41.3X3A-T41.3X3D,T41.3X4A-T41.3X4D,  
T41.3X5A-T41.3X5D,T41.41XA-T41.41XD,T41.42XA-T41.42XD,T41.43XA-T41.43XD,T41.44XA-T41.44XD,  
T41.45XA-T41.45XD,T41.5X1A-T41.5X1D,T41.5X2A-T41.5X2D,T41.5X3A-T41.5X3D,T41.5X4A-T41.5X4D,  
T41.5X5A-T41.5X5D,T42.0X1A-T42.0X1D,T42.0X2A-T42.0X2D,T42.0X3A-T42.0X3D,T42.0X4A-T42.0X4D,  
T42.0X5A-T42.0X5D,T42.1X1A-T42.1X1D,T42.1X2A-T42.1X2D,T42.1X3A-T42.1X3D,T42.1X4A-T42.1X4D,  
T42.1X5A-T42.1X5D,T42.2X1A-T42.2X1D,T42.2X2A-T42.2X2D,T42.2X3A-T42.2X3D,T42.2X4A-T42.2X4D,  
T42.2X5A-T42.2X5D,T42.3X1A-T42.3X1D,T42.3X2A-T42.3X2D,T42.3X3A-T42.3X3D,T42.3X4A-T42.3X4D,  
T42.3X5A-T42.3X5D,T42.4X1A-T42.4X1D,T42.4X2A-T42.4X2D,T42.4X3A-T42.4X3D,T42.4X4A-T42.4X4D,  
T42.4X5A-T42.4X5D,T42.5X1A-T42.5X1D,T42.5X2A-T42.5X2D,T42.5X3A-T42.5X3D,T42.5X4A-T42.5X4D,  
T42.5X5A-T42.5X5D,T42.6X1A-T42.6X1D,T42.6X2A-T42.6X2D,T42.6X3A-T42.6X3D,T42.6X4A-T42.6X4D,  
T42.6X5A-T42.6X5D,T42.71XA-T42.71XD,T42.72XA-T42.72XD,T42.73XA-T42.73XD,T42.74XA-T42.74XD,  
T42.75XA-T42.75XD,T42.8X1A-T42.8X1D,T42.8X2A-T42.8X2D,T42.8X3A-T42.8X3D,T42.8X4A-T42.8X4D,  
T42.8X5A-T42.8X5D,T43.011A-T43.011D,T43.012A-T43.012D,T43.013A-T43.013D,T43.014A-T43.014D,  
T43.015A-T43.015D,T43.021A-T43.021D,T43.022A-T43.022D,T43.023A-T43.023D,T43.024A-T43.024D,  
T43.025A-T43.025D,T43.1X1A-T43.1X1D,T43.1X2A-T43.1X2D,T43.1X3A-T43.1X3D,T43.1X4A-T43.1X4D,  
T43.1X5A-T43.1X5D,T43.201A-T43.201D,T43.202A-T43.202D,T43.203A-T43.203D,T43.204A-T43.204D,  
T43.205A-T43.205D,T43.211A-T43.211D,T43.212A-T43.212D,T43.213A-T43.213D,T43.214A-T43.214D,  
T43.215A-T43.215D,T43.221A-T43.221D,T43.222A-T43.222D,T43.223A-T43.223D,T43.224A-T43.224D,  
T43.225A-T43.225D,T43.291A-T43.291D,T43.292A-T43.292D,T43.293A-T43.293D,T43.294A-T43.294D,



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T43.295A-T43.295D, T43.3X1A-T43.3X1D, T43.3X2A-T43.3X2D, T43.3X3A-T43.3X3D, T43.3X4A-T43.3X4D, T43.3X5A-T43.3X5D, T43.4X1A-T43.4X1D, T43.4X2A-T43.4X2D, T43.4X3A-T43.4X3D, T43.4X4A-T43.4X4D, T43.4X5A-T43.4X5D, T43.501A-T43.501D, T43.502A-T43.502D, T43.503A-T43.503D, T43.504A-T43.504D, T43.505A-T43.505D, T43.591A-T43.591D, T43.592A-T43.592D, T43.593A-T43.593D, T43.594A-T43.594D, T43.595A-T43.595D, T43.601A-T43.601D, T43.602A-T43.602D, T43.603A-T43.603D, T43.604A-T43.604D, T43.605A-T43.605D, T43.611A-T43.611D, T43.612A-T43.612D, T43.613A-T43.613D, T43.614A-T43.614D, T43.615A-T43.615D, T43.621A-T43.621D, T43.622A-T43.622D, T43.623A-T43.623D, T43.624A-T43.624D, T43.625A-T43.625D, T43.631A-T43.631D, T43.632A-T43.632D, T43.633A-T43.633D, T43.634A-T43.634D, T43.635A-T43.635D, T43.691A-T43.691D, T43.692A-T43.692D, T43.693A-T43.693D, T43.694A-T43.694D, T43.695A-T43.695D, T43.8X1A-T43.8X1D, T43.8X2A-T43.8X2D, T43.8X3A-T43.8X3D, T43.8X4A-T43.8X4D, T43.8X5A-T43.8X5D, T43.91XA-T43.91XD, T43.92XA-T43.92XD, T43.93XA-T43.93XD, T43.94XA-T43.94XD, T43.95XA-T43.95XD, T44.0X1A-T44.0X1D, T44.0X2A-T44.0X2D, T44.0X3A-T44.0X3D, T44.0X4A-T44.0X4D, T44.0X5A-T44.0X5D, T44.1X1A-T44.1X1D, T44.1X2A-T44.1X2D, T44.1X3A-T44.1X3D, T44.1X4A-T44.1X4D, T44.1X5A-T44.1X5D, T44.2X1A-T44.2X1D, T44.2X2A-T44.2X2D, T44.2X3A-T44.2X3D, T44.2X4A-T44.2X4D, T44.2X5A-T44.2X5D, T44.3X1A-T44.3X1D, T44.3X2A-T44.3X2D, T44.3X3A-T44.3X3D, T44.3X4A-T44.3X4D, T44.3X5A-T44.3X5D, T44.4X1A-T44.4X1D, T44.4X2A-T44.4X2D, T44.4X3A-T44.4X3D, T44.4X4A-T44.4X4D, T44.4X5A-T44.4X5D, T44.5X1A-T44.5X1D, T44.5X2A-T44.5X2D, T44.5X3A-T44.5X3D, T44.5X4A-T44.5X4D, T44.5X5A-T44.5X5D, T44.6X1A-T44.6X1D, T44.6X2A-T44.6X2D, T44.6X3A-T44.6X3D, T44.6X4A-T44.6X4D, T44.6X5A-T44.6X5D, T44.7X1A-T44.7X1D, T44.7X2A-T44.7X2D, T44.7X3A-T44.7X3D, T44.7X4A-T44.7X4D, T44.7X5A-T44.7X5D, T44.8X1A-T44.8X1D, T44.8X2A-T44.8X2D, T44.8X3A-T44.8X3D, T44.8X4A-T44.8X4D, T44.8X5A-T44.8X5D, T44.901A-T44.901D, T44.902A-T44.902D, T44.903A-T44.903D, 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T47.4X5A-T47.4X5D, T47.5X1A-T47.5X1D, T47.5X2A-T47.5X2D, T47.5X3A-T47.5X3D, T47.5X4A-T47.5X4D, T47.5X5A-T47.5X5D, T47.6X1A-T47.6X1D, T47.6X2A-T47.6X2D, T47.6X3A-T47.6X3D, T47.6X4A-T47.6X4D, T47.6X5A-T47.6X5D, T47.7X1A-T47.7X1D, T47.7X2A-T47.7X2D, T47.7X3A-T47.7X3D, T47.7X4A-T47.7X4D, T47.7X5A-T47.7X5D, T47.8X1A-T47.8X1D, T47.8X2A-T47.8X2D, T47.8X3A-T47.8X3D, T47.8X4A-T47.8X4D, T47.8X5A-T47.8X5D, T47.91XA-T47.91XD, T47.92XA-T47.92XD, T47.93XA-T47.93XD, T47.94XA-T47.94XD, T47.95XA-T47.95XD, T48.0X1A-T48.0X1D, T48.0X2A-T48.0X2D, T48.0X3A-T48.0X3D, T48.0X4A-T48.0X4D, T48.0X5A-T48.0X5D, T48.1X1A-T48.1X1D, T48.1X2A-T48.1X2D, T48.1X3A-T48.1X3D, T48.1X4A-T48.1X4D, T48.1X5A-T48.1X5D, T48.201A-T48.201D, T48.202A-T48.202D, T48.203A-T48.203D, T48.204A-T48.204D, T48.205A-T48.205D, T48.291A-T48.291D, T48.292A-T48.292D, T48.293A-T48.293D, T48.294A-T48.294D, T48.295A-T48.295D, T48.3X1A-T48.3X1D, T48.3X2A-T48.3X2D, T48.3X3A-T48.3X3D, T48.3X4A-T48.3X4D, T48.3X5A-T48.3X5D, T48.4X1A-T48.4X1D, T48.4X2A-T48.4X2D, T48.4X3A-T48.4X3D, T48.4X4A-T48.4X4D, T48.4X5A-T48.4X5D, T48.5X1A-T48.5X1D, T48.5X2A-T48.5X2D, T48.5X3A-T48.5X3D, T48.5X4A-T48.5X4D, T48.5X5A-T48.5X5D, T48.6X1A-T48.6X1D, T48.6X2A-T48.6X2D, T48.6X3A-T48.6X3D, T48.6X4A-T48.6X4D, T48.6X5A-T48.6X5D, T48.901A-T48.901D, T48.902A-T48.902D, T48.903A-T48.903D, T48.904A-T48.904D, T48.905A-T48.905D, T48.991A-T48.991D, T48.992A-T48.992D, T48.993A-T48.993D, T48.994A-T48.994D, T48.995A-T48.995D, T49.0X1A-T49.0X1D, T49.0X2A-T49.0X2D, T49.0X3A-T49.0X3D, T49.0X4A-T49.0X4D, T49.0X5A-T49.0X5D, T49.1X1A-T49.1X1D, T49.1X2A-T49.1X2D, T49.1X3A-T49.1X3D, T49.1X4A-T49.1X4D, T49.1X5A-T49.1X5D, T49.2X1A-T49.2X1D, T49.2X2A-T49.2X2D, T49.2X3A-T49.2X3D, T49.2X4A-T49.2X4D, T49.2X5A-T49.2X5D, T49.3X1A-T49.3X1D, T49.3X2A-T49.3X2D, T49.3X3A-T49.3X3D, T49.3X4A-T49.3X4D, T49.3X5A-T49.3X5D, T49.4X1A-T49.4X1D, T49.4X2A-T49.4X2D, T49.4X3A-T49.4X3D, T49.4X4A-T49.4X4D,



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T49.4X5A-T49.4X5D,T49.5X1A-T49.5X1D,T49.5X2A-T49.5X2D,T49.5X3A-T49.5X3D,T49.5X4A-T49.5X4D,  
T49.5X5A-T49.5X5D,T49.6X1A-T49.6X1D,T49.6X2A-T49.6X2D,T49.6X3A-T49.6X3D,T49.6X4A-T49.6X4D,  
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PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

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CPT: 43241, 43247, 49435, 49436, 90935-90947, 90989-90997, 93792, 93793, 94640, 95017, 95018, 95076, 95079, 96150-96155, 98966-98969, 99051, 99060, 99070, 99078, 99175, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607

HCPCS: G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514, S9355

Line: 104

Condition: BOTULISM (See Guideline Notes 64,65)

Treatment: MEDICAL THERAPY

ICD-10: A05.1, A48.51-A48.52

CPT: 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607

HCPCS: G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

- Line: 105**  
Condition: TETRALOGY OF FALLOT (TOF); CONGENITAL VENOUS ABNORMALITIES (See Guideline Notes 64,65)  
Treatment: REPAIR  
ICD-10: Q21.3,Q25.5-Q25.6,Q25.71-Q25.79,Q26.0-Q26.1,Q26.3-Q26.9,Z79.01  
CPT: 33606,33608,33620,33621,33692-33697,33726,33735-33750,33764,33917,33924-33926,33946-33966,33969,33984-33989,34502,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 106**  
Condition: CONGENITAL STENOSIS AND INSUFFICIENCY OF AORTIC VALVE (See Guideline Notes 64,65)  
Treatment: SURGICAL VALVE REPLACEMENT/VALVULOPLASTY  
ICD-10: Q23.0-Q23.1,Q24.4,Q25.3  
CPT: 33361-33417,33496,33530,33620,33621,33946-33966,33969,33984-33989,37246,37247,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 107**  
Condition: GIANT CELL ARTERITIS, POLYMYALGIA RHEUMATICA AND KAWASAKI DISEASE (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: M30.3,M31.0,M31.4-M31.6,M35.3  
CPT: 36514,36516,37609,90284,92002-92014,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 108**  
Condition: FRACTURE OF RIBS AND STERNUM, OPEN (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: S22.20XB,S22.21XB,S22.22XB,S22.23XB,S22.24XB,S22.31XB,S22.32XB,S22.39XB,S22.41XB,S22.42XB,S22.43XB,S22.49XB,S22.5XXB,S22.9XXB  
CPT: 11010-11012,21811-21813,21825,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 109**  
Condition: SUBACUTE MENINGITIS (E.G., TUBERCULOSIS, CRYPTOCOCCOSIS) (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A01.01,A17.0-A17.1,A17.81-A17.89,A27.81,A42.81-A42.82,B37.5,B45.8,B57.40-B57.49,B58.2,B60.0,G02,G03.0-G03.1,G03.8-G03.9  
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 110**  
Condition: COAGULATION DEFECTS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: D66-D67,D68.0-D68.2,D68.311-D68.4,D68.8-D68.9,M25.00,M25.011-M25.08,Z14.02  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9345



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

- Line: 111**  
Condition: CONGENITAL HEART BLOCK; OTHER OBSTRUCTIVE ANOMALIES OF HEART (See Guideline Notes 49,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: Q23.8-Q23.9,Q24.6-Q24.8,Q28.8,Z45.010-Z45.09,Z79.01  
CPT: 33202-33249,33262-33264,33270-33273,33418-33496,33530,33620,33621,33946-33966,33969,33984-33989,75557-75565,75573,92960-92971,92978-92998,93279-93284,93286-93289,93292-93296,93355,93644,93745,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,K0606-K0609
- Line: 112**  
Condition: CANCER OF TESTIS (See Guideline Notes 7,11,12,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C62.00-C62.92,D40.10-D40.12,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.47  
CPT: 32553,38564,38571-38573,38780,49327,49411,49412,54512-54535,54660,54690,77261-77290,77295,77300,77306,77307,77321-77370,77385-77387,77401-77417,77424-77431,77469,77470,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537
- Line: 113**  
Condition: CANCER OF EYE AND ORBIT (See Guideline Notes 7,11,12,16,19,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C69.00-C69.92,D09.20-D09.22,D48.7,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.840  
CPT: 11420,11440,13132,20969,32553,49411,65091,65101-65114,65435,65450,65900,66600,66605,66770,67208-67218,67412,67414,67445,68135,68320-68328,68335,68340,77014,77261-77295,77300-77370,77385-77387,77401-77432,77469,77470,77520-77525,77750,77789,78816,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,96150-96155,96377,96405,96406,96420-96440,96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537
- Line: 114**  
Condition: APLASTIC ANEMIAS; AGRANULOCYTOSIS (See Guideline Notes 7,11,12,14)  
Treatment: BONE MARROW TRANSPLANT  
ICD-10: D60.0-D60.9,D61.01-D61.3,D61.810,D61.82-D61.9,T86.01-T86.09,Z48.290,Z52.000-Z52.008,Z52.090-Z52.098,Z52.3  
CPT: 36680,38204-38215,38240,38242,86825,86826,90284,93792,93793,96377,96405,96406,96420-96440,96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S2142,S2150,S9537
- Line: 115**  
Condition: CHRONIC MYELOID LEUKEMIA (See Guideline Notes 7,11,12)  
Treatment: MEDICAL THERAPY, WHICH INCLUDES CHEMOTHERAPY, RADIATION AND RADIONUCLIDE THERAPY  
ICD-10: C92.10-C92.32,D61.810,G89.3,Z51.0,Z51.12  
CPT: 32553,49411,77014,77261-77290,77295,77300,77306,77307,77321-77370,77385-77387,77401-77417,77424-77427,77469,79101,90284,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99195,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537
- Line: 116**  
Condition: HODGKIN'S DISEASE (See Guideline Notes 7,11,12,14,19)  
Treatment: BONE MARROW TRANSPLANT  
ICD-10: C81.00-C81.99,D61.810,T86.01-T86.09,T86.5,Z48.290,Z52.000-Z52.098,Z52.3,Z85.71  
CPT: 36680,38204-38215,38230-38243,78811-78816,86825-86835,90284,93792,93793,96377,96405,96406,96420-96440,96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S2142,S2150,S9537



*PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)*

**Line: 117**  
Condition: FOREIGN BODY IN PHARYNX, LARYNX, TRACHEA, BRONCHUS AND ESOPHAGUS (See Guideline Notes 64,65)  
Treatment: REMOVAL OF FOREIGN BODY  
ICD-10: T17.200A-T17.200D,T17.208A-T17.208D,T17.210A-T17.210D,T17.220A-T17.220D,T17.228A-T17.228D,T17.290A-T17.290D,T17.298A-T17.298D,T17.300A-T17.300D,T17.308A-T17.308D,T17.310A-T17.310D,T17.320A-T17.320D,T17.328A-T17.328D,T17.390A-T17.390D,T17.398A-T17.398D,T17.400A-T17.400D,T17.408A-T17.408D,T17.410A-T17.410D,T17.418A-T17.418D,T17.420A-T17.420D,T17.428A-T17.428D,T17.490A-T17.490D,T17.498A-T17.498D,T17.500A-T17.500D,T17.508A-T17.508D,T17.510A-T17.510D,T17.518A-T17.518D,T17.520A-T17.520D,T17.528A-T17.528D,T17.590A-T17.590D,T17.598A-T17.598D,T17.800A-T17.800D,T17.808A-T17.808D,T17.810A-T17.810D,T17.820A-T17.820D,T17.828A-T17.828D,T17.890A-T17.890D,T17.898A-T17.898D,T17.900A-T17.900D,T17.908A-T17.908D,T17.910A-T17.910D,T17.920A-T17.920D,T17.928A-T17.928D,T17.990A-T17.990D,T17.998A-T17.998D,T18.0XXA-T18.0XXD,T18.100A-T18.100D,T18.108A-T18.108D,T18.110A-T18.110D,T18.120A-T18.120D,T18.128A-T18.128D,T18.190A-T18.190D,T18.198A-T18.198D  
CPT: 31511,31512,31530,31531,31635,32150,32151,40804,41805,42809,43020,43045,43194,43215,43247,43249,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 118**  
Condition: NUTRITIONAL DEFICIENCIES (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: D50.0-D50.9,D51.0-D51.9,D52.0-D52.9,D53.0-D53.9,D64.0-D64.3,D81.818-D81.819,E40-E43,E44.0-E44.1,E45-E46,E50.0-E50.9,E51.11-E51.12,E51.8-E51.9,E52,E53.0-E53.9,E54,E55.0-E55.9,E56.0-E56.8,E58-E60,E61.0-E61.6,E63.0-E63.8  
CPT: 93792,93793,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99468,99469,99477-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 119**  
Condition: ATRIAL SEPTAL DEFECT, SECUNDUM (See Guideline Notes 64,65)  
Treatment: REPAIR SEPTAL DEFECT  
ICD-10: Q21.1  
CPT: 33641,33647,33946-33966,33969,33984-33989,92960-92971,92978-92998,93355,93580,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 120**  
Condition: CHOANAL ATRESIA (See Guideline Notes 64,65)  
Treatment: REPAIR OF CHOANAL ATRESIA  
ICD-10: Q30.0  
CPT: 30520-30545,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 121**  
Condition: ABUSE AND NEGLECT (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: T73.0XXA-T73.0XXD,T73.1XXA-T73.1XXD,T74.01XA-T74.01XD,T74.02XA-T74.02XD,T74.11XA-T74.11XD,T74.12XA-T74.12XD,T74.21XA-T74.21XD,T74.22XA-T74.22XD,T74.31XA-T74.31XD,T74.32XA-T74.32XD,T74.4XXA-T74.4XXD,T74.91XA-T74.91XD,T74.92XA-T74.92XD,T76.01XA-T76.01XD,T76.02XA-T76.02XD,T76.11XA-T76.11XD,T76.12XA-T76.12XD,T76.21XA-T76.21XD,T76.22XA-T76.22XD,T76.31XA-T76.31XD,T76.32XA-T76.32XD,T76.91XA-T76.91XD,T76.92XA-T76.92XD,Z04.41-Z04.42,Z04.71-Z04.72,Z69.010-Z69.020,Z69.11,Z69.81  
CPT: 46700,46706,46707,56800,56810,57023,57200,57210,57415,90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,H0038,H2027



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

- Line: 122**  
Condition: ATTENTION DEFICIT/HYPERACTIVITY DISORDERS (See Guideline Notes 20,64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F90.0-F90.9  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0023,H0032-H0038,H0045,H2010,H2012-H2014,H2021,H2022,H2027,H2032,S5151,S9125,S9484,T1005
- Line: 123**  
Condition: MALARIA, CHAGAS' DISEASE AND TRYPANOSOMIASIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: B50.0-B50.9,B51.8-B51.9,B52.0-B52.9,B53.0-B53.8,B54,B56.0-B56.9,B57.1,B57.30-B57.39,B57.5  
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 124**  
Condition: ANAPHYLACTIC SHOCK; EDEMA OF LARYNX (See Guideline Notes 64,65,156)  
Treatment: MEDICAL THERAPY  
ICD-10: J38.4,T78.00XA-T78.00XD,T78.01XA-T78.01XD,T78.02XA-T78.02XD,T78.03XA-T78.03XD,T78.04XA-T78.04XD,T78.05XA-T78.05XD,T78.06XA-T78.06XD,T78.07XA-T78.07XD,T78.08XA-T78.08XD,T78.09XA-T78.09XD,T78.2XXA-T78.2XXD,T88.2XXA-T88.2XXD,T88.6XXA-T88.6XXD,Z51.6  
CPT: 86003,86008,86486,93792,93793,95004,95017-95180,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 125**  
Condition: THYROTOXICOSIS WITH OR WITHOUT GOITER, ENDOCRINE EXOPHTHALMOS; CHRONIC THYROIDITIS (See Guideline Notes 12,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT WHICH INCLUDES RADIATION THERAPY  
ICD-10: E05.00-E05.91,E06.0-E06.9,Z51.0  
CPT: 32553,36514,36516,49411,60210-60240,60270,60271,60512,67414,67440,67445,77014,77261-77295,77300-77307,77331-77338,77385-77387,77401-77427,77469,77470,79005-79445,92002-92014,92081,92082,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017
- Line: 126**  
Condition: BENIGN NEOPLASM OF THE BRAIN AND SPINAL CORD (See Guideline Notes 7,11,16,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: D18.02,D32.0-D32.9,D33.0-D33.7,D35.2-D35.3,D44.3-D44.4,D61.810,G89.3,H47.141-H47.149,Q85.00-Q85.09,Q85.8-Q85.9,Z45.49,Z51.0,Z51.12,Z86.011  
CPT: 12034,32553,49411,61312-61330,61333-61512,61516-61521,61524-61530,61534,61536-61564,61571-61626,61781,61782,61796-61800,62100,62140-62160,62163-62165,62223,62272,63265,63275-63295,63615,77014,77261-77295,77300-77307,77321-77372,77385-77387,77402-77432,77469,77470,77520-77763,77770-77790,79005-79445,92002-92014,92081-92083,93792,93793,95990,96150-96155,96377,96405,96406,96420-96440,96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017
- Line: 127**  
Condition: ACUTE KIDNEY INJURY (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY INCLUDING DIALYSIS  
ICD-10: N00.0-N00.9,N01.0-N01.9,N17.0-N17.9,Z49.01-Z49.32  
CPT: 36514,36516,36818-36821,36831-36838,36901-36909,49324-49326,49421,49422,49435,49436,90935-90947,90989-90997,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9339,S9537



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**Line: 128**  
Condition: COMMON TRUNCUS (See Guideline Notes 64,65)  
Treatment: TOTAL REPAIR/REPLANT ARTERY  
ICD-10: Q20.0  
CPT: 33608,33620,33621,33786,33788,33813,33814,33946-33966,33969,33984-33989,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 129**  
Condition: GRANULOMATOSIS WITH POLYANGIITIS (See Guideline Notes 12,16,64,65)  
Treatment: MEDICAL THERAPY, WHICH INCLUDES RADIATION THERAPY  
ICD-10: G89.3,M30.1,M31.2,M31.30-M31.31,M31.7,Z51.0  
CPT: 32553,36514,36516,49411,77014,77261-77295,77300-77307,77331-77338,77385-77387,77401-77427,77469,77470,77520-77525,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017

**Line: 130**  
Condition: TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION (See Guideline Notes 14,64,65)  
Treatment: COMPLETE REPAIR  
ICD-10: Q24.2,Q26.2  
CPT: 33620,33621,33724,33730,33732,33946-33966,33969,33984-33989,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 131**  
Condition: CRUSH INJURIES OTHER THAN DIGITS; COMPARTMENT SYNDROME (See Guideline Notes 6,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: M60.000-M60.005,M60.011-M60.09,M62.82,M79.A11-M79.A9,S07.0XXA-S07.0XXD,S07.1XXA-S07.1XXD,S07.8XXA-S07.8XXD,S07.9XXA-S07.9XXD,S17.0XXA-S17.0XXD,S17.8XXA-S17.8XXD,S17.9XXA-S17.9XXD,S28.0XXA-S28.0XXD,S35.8X1A-S35.8X1D,S35.8X8A-S35.8X8D,S35.8X9A-S35.8X9D,S35.90XA-S35.90XD,S35.91XA-S35.91XD,S35.99XA-S35.99XD,S38.001A-S38.001D,S38.002A-S38.002D,S38.01XA-S38.01XD,S38.02XA-S38.02XD,S38.03XA-S38.03XD,S38.1XXA-S38.1XXD,S47.1XXA-S47.1XXD,S47.2XXA-S47.2XXD,S47.9XXA-S47.9XXD,S57.00XA-S57.00XD,S57.01XA-S57.01XD,S57.02XA-S57.02XD,S57.80XA-S57.80XD,S57.81XA-S57.81XD,S57.82XA-S57.82XD,S67.20XA-S67.20XD,S67.21XA-S67.21XD,S67.22XA-S67.22XD,S67.30XA-S67.30XD,S67.31XA-S67.31XD,S67.32XA-S67.32XD,S67.40XA-S67.40XD,S67.41XA-S67.41XD,S67.42XA-S67.42XD,S67.90XA-S67.90XD,S67.91XA-S67.91XD,S67.92XA-S67.92XD,S77.00XA-S77.00XD,S77.01XA-S77.01XD,S77.02XA-S77.02XD,S77.10XA-S77.10XD,S77.11XA-S77.11XD,S77.12XA-S77.12XD,S77.20XA-S77.20XD,S77.21XA-S77.21XD,S77.22XA-S77.22XD,S87.00XA-S87.00XD,S87.01XA-S87.01XD,S87.02XA-S87.02XD,S87.80XA-S87.80XD,S87.81XA-S87.81XD,S87.82XA-S87.82XD,S97.00XA-S97.00XD,S97.01XA-S97.01XD,S97.02XA-S97.02XD,S97.80XA-S97.80XD,S97.81XA-S97.81XD,S97.82XA-S97.82XD,T79.5XXA-T79.5XXD,T79.6XXA-T79.6XXD,T79.A0XA-T79.A0XD,T79.A11A-T79.A11D,T79.A12A-T79.A12D,T79.A19A-T79.A19D,T79.A21A-T79.A21D,T79.A22A-T79.A22D,T79.A29A-T79.A29D,T79.A3XA-T79.A3XD,T79.A9XA-T79.A9XD,T79.8XXA-T79.8XXD,T79.9XXA-T79.9XXD  
CPT: 11043-11047,11740,20101-20103,20950,20972,21627,21630,23395,24495,25020-25025,25274,25295,25320,25335,25337,25390-25393,25441-25447,25450-25492,25810-25830,26037,26357-26390,26437,27025,27027,27057,27305,27465-27468,27496-27499,27600-27602,27656-27659,27665,27695-27698,27892-27894,28008,35141,35221,36514,36516,37616,37617,54230,74445,92960-92971,92978-92998,93792-93798,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 132**  
Condition: OPEN FRACTURE/DISLOCATION OF EXTREMITIES (See Guideline Notes 6,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: S42.001B,S42.002B,S42.009B,S42.011B,S42.012B,S42.013B,S42.014B,S42.015B,S42.016B,S42.017B,S42.018B,S42.019B,S42.021B,S42.022B,S42.023B,S42.024B,S42.025B,S42.026B,S42.031B,S42.032B,S42.033B,S42.034B,S42.035B,S42.036B,S42.101B,S42.102B,S42.109B,S42.111B,S42.112B,S42.113B,S42.114B,S42.115B,S42.116B,S42.121B,S42.122B,S42.123B,S42.124B,S42.125B,S42.126B,S42.131B,S42.132B,S42.133B,S42.134B,S42.135B,S42.136B,S42.141B,S42.142B,S42.143B,S42.144B,S42.145B,S42.146B,S42.151B,S42.152B,S42.153B,S42.154B,S42.155B,S42.156B,S42.191B,S42.192B,S42.199B,S42.201B,S42.202B,S42.209B,S42.211B,S42.212B,S42.213B,S42.214B,S42.215B,S42.216B,S42.221B,S42.222B,S42.223B,S42.224B,S42.225B,S42.226B,S42.231B,S42.232B,S42.239B,S42.241B,S42.242B,



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S42.249B,S42.251B,S42.252B,S42.253B,S42.254B,S42.255B,S42.256B,S42.261B,S42.262B,S42.263B,  
S42.264B,S42.265B,S42.266B,S42.291B,S42.292B,S42.293B,S42.294B,S42.295B,S42.296B,S42.301B,  
S42.302B,S42.309B,S42.321B,S42.322B,S42.323B,S42.324B,S42.325B,S42.326B,S42.331B,S42.332B,  
S42.333B,S42.334B,S42.335B,S42.336B,S42.341B,S42.342B,S42.343B,S42.344B,S42.345B,S42.346B,  
S42.351B,S42.352B,S42.353B,S42.354B,S42.355B,S42.356B,S42.361B,S42.362B,S42.363B,S42.364B,  
S42.365B,S42.366B,S42.391B,S42.392B,S42.399B,S42.401B,S42.402B,S42.409B,S42.411B,S42.412B,  
S42.413B,S42.414B,S42.415B,S42.416B,S42.421B,S42.422B,S42.423B,S42.424B,S42.425B,S42.426B,  
S42.431B,S42.432B,S42.433B,S42.434B,S42.435B,S42.436B,S42.441B,S42.442B,S42.443B,S42.444B,  
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S42.456B,S42.461B,S42.462B,S42.463B,S42.464B,S42.465B,S42.466B,S42.471B,S42.472B,S42.473B,  
S42.474B,S42.475B,S42.476B,S42.491B,S42.492B,S42.493B,S42.494B,S42.495B,S42.496B,S42.90XB,  
S42.91XB,S42.92XB,S52.001B-S52.001C,S52.001E-S52.001F,S52.001H-S52.001J,S52.002B-S52.002C,  
S52.002E-S52.002F,S52.002H-S52.002J,S52.009B-S52.009C,S52.009E-S52.009F,S52.009H-S52.009J,  
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S52.022H-S52.022J,S52.023B-S52.023C,S52.023E-S52.023F,S52.023H-S52.023J,S52.024B-S52.024C,  
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S52.026B-S52.026C,S52.026E-S52.026F,S52.026H-S52.026J,S52.031B-S52.031C,S52.031E-S52.031F,  
S52.031H-S52.031J,S52.032B-S52.032C,S52.032E-S52.032F,S52.032H-S52.032J,S52.033B-S52.033C,  
S52.033E-S52.033F,S52.033H-S52.033J,S52.034B-S52.034C,S52.034E-S52.034F,S52.034H-S52.034J,  
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S52.042E-S52.042F,S52.042H-S52.042J,S52.043B-S52.043C,S52.043E-S52.043F,S52.043H-S52.043J,  
S52.044B-S52.044C,S52.044E-S52.044F,S52.044H-S52.044J,S52.045B-S52.045C,S52.045E-S52.045F,  
S52.045H-S52.045J,S52.046B-S52.046C,S52.046E-S52.046F,S52.046H-S52.046J,S52.091B-S52.091C,  
S52.091E-S52.091F,S52.091H-S52.091J,S52.092B-S52.092C,S52.092E-S52.092F,S52.092H-S52.092J,  
S52.099B-S52.099C,S52.099E-S52.099F,S52.099H-S52.099J,S52.101B-S52.101C,S52.101E-S52.101F,  
S52.101H-S52.101J,S52.102B-S52.102C,S52.102E-S52.102F,S52.102H-S52.102J,S52.109B-S52.109C,  
S52.109E-S52.109F,S52.109H-S52.109J,S52.121B-S52.121C,S52.121E-S52.121F,S52.121H-S52.121J,  
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S52.123H-S52.123J,S52.124B-S52.124C,S52.124E-S52.124F,S52.124H-S52.124J,S52.125B-S52.125C,  
S52.125E-S52.125F,S52.125H-S52.125J,S52.126B-S52.126C,S52.126E-S52.126F,S52.126H-S52.126J,  
S52.131B-S52.131C,S52.131E-S52.131F,S52.131H-S52.131J,S52.132B-S52.132C,S52.132E-S52.132F,  
S52.132H-S52.132J,S52.133B-S52.133C,S52.133E-S52.133F,S52.133H-S52.133J,S52.134B-S52.134C,  
S52.134E-S52.134F,S52.134H-S52.134J,S52.135B-S52.135C,S52.135E-S52.135F,S52.135H-S52.135J,  
S52.136B-S52.136C,S52.136E-S52.136F,S52.136H-S52.136J,S52.181B-S52.181C,S52.181E-S52.181F,  
S52.181H-S52.181J,S52.182B-S52.182C,S52.182E-S52.182F,S52.182H-S52.182J,S52.189B-S52.189C,  
S52.189E-S52.189F,S52.189H-S52.189J,S52.201B-S52.201C,S52.201E-S52.201F,S52.201H-S52.201J,  
S52.202B-S52.202C,S52.202E-S52.202F,S52.202H-S52.202J,S52.209B-S52.209C,S52.209E-S52.209F,  
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S52.266H-S52.266J,S52.271B-S52.271C,S52.271E-S52.271F,S52.271H-S52.271J,S52.272B-S52.272C,  
S52.272E-S52.272F,S52.272H-S52.272J,S52.279B-S52.279C,S52.279E-S52.279F,S52.279H-S52.279J,  
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S52.299B-S52.299C,S52.299E-S52.299F,S52.299H-S52.299J,S52.301B-S52.301C,S52.301E-S52.301F,  
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S72.325J,S72.326B-S72.326C,S72.326E-S72.326F,S72.326H-S72.326J,S72.331B-S72.331C,S72.331E-S72.331F,S72.331H-S72.331J,S72.332B-S72.332C,S72.332E-S72.332F,S72.332H-S72.332J,S72.333B-S72.333C,S72.333E-S72.333F,S72.333H-S72.333J,S72.334B-S72.334C,S72.334E-S72.334F,S72.334H-S72.334J,S72.335B-S72.335C,S72.335E-S72.335F,S72.335H-S72.335J,S72.336B-S72.336C,S72.336E-S72.336F,S72.336H-S72.336J,S72.341B-S72.341C,S72.341E-S72.341F,S72.341H-S72.341J,S72.342B-S72.342C,S72.342E-S72.342F,S72.342H-S72.342J,S72.343B-S72.343C,S72.343E-S72.343F,S72.343H-S72.343J,S72.344B-S72.344C,S72.344E-S72.344F,S72.344H-S72.344J,S72.345B-S72.345C,S72.345E-S72.345F,S72.345H-S72.345J,S72.346B-S72.346C,S72.346E-S72.346F,S72.346H-S72.346J,S72.351B-S72.351C,S72.351E-S72.351F,S72.351H-S72.351J,S72.352B-S72.352C,S72.352E-S72.352F,S72.352H-S72.352J,S72.353B-S72.353C,S72.353E-S72.353F,S72.353H-S72.353J,S72.354B-S72.354C,S72.354E-S72.354F,S72.354H-S72.354J,S72.355B-S72.355C,S72.355E-S72.355F,S72.355H-S72.355J,S72.356B-S72.356C,S72.356E-S72.356F,S72.356H-S72.356J,S72.361B-S72.361C,S72.361E-S72.361F,S72.361H-S72.361J,S72.362B-S72.362C,S72.362E-S72.362F,S72.362H-S72.362J,S72.363B-S72.363C,S72.363E-S72.363F,S72.363H-S72.363J,S72.364B-S72.364C,S72.364E-S72.364F,S72.364H-S72.364J,S72.365B-S72.365C,S72.365E-S72.365F,S72.365H-S72.365J,S72.366B-S72.366C,S72.366E-S72.366F,S72.366H-S72.366J,S72.391B-S72.391C,S72.391E-S72.391F,S72.391H-S72.391J,S72.392B-S72.392C,S72.392E-S72.392F,S72.392H-S72.392J,S72.399B-S72.399C,S72.399E-S72.399F,S72.399H-S72.399J,S72.401B-S72.401C,S72.401E-S72.401F,S72.401H-S72.401J,S72.402B-S72.402C,S72.402E-S72.402F,S72.402H-S72.402J,S72.409B-S72.409C,S72.409E-S72.409F,S72.409H-S72.409J,S72.411B-S72.411C,S72.411E-S72.411F,S72.411H-S72.411J,S72.412B-S72.412C,S72.412E-S72.412F,S72.412H-S72.412J,S72.413B-S72.413C,S72.413E-S72.413F,S72.413H-S72.413J,S72.414B-S72.414C,S72.414E-S72.414F,S72.414H-S72.414J,S72.415B-S72.415C,S72.415E-S72.415F,S72.415H-S72.415J,S72.416B-S72.416C,S72.416E-S72.416F,S72.416H-S72.416J,S72.421B-S72.421C,S72.421E-S72.421F,S72.421H-S72.421J,S72.422B-S72.422C,S72.422E-S72.422F,S72.422H-S72.422J,S72.423B-S72.423C,S72.423E-S72.423F,S72.423H-S72.423J,S72.424B-S72.424C,S72.424E-S72.424F,S72.424H-S72.424J,S72.425B-S72.425C,S72.425E-S72.425F,S72.425H-S72.425J,S72.426B-S72.426C,S72.426E-S72.426F,S72.426H-S72.426J,S72.431B-S72.431C,S72.431E-S72.431F,S72.431H-S72.431J,S72.432B-S72.432C,S72.432E-S72.432F,S72.432H-S72.432J,S72.433B-S72.433C,S72.433E-S72.433F,S72.433H-S72.433J,S72.434B-S72.434C,S72.434E-S72.434F,S72.434H-S72.434J,S72.435B-S72.435C,S72.435E-S72.435F,S72.435H-S72.435J,S72.436B-S72.436C,S72.436E-S72.436F,S72.436H-S72.436J,S72.441B-S72.441C,S72.441E-S72.441F,S72.441H-S72.441J,S72.442B-S72.442C,S72.442E-S72.442F,S72.442H-S72.442J,S72.443B-S72.443C,S72.443E-S72.443F,S72.443H-S72.443J,S72.444B-S72.444C,S72.444E-S72.444F,S72.444H-S72.444J,S72.445B-S72.445C,S72.445E-S72.445F,S72.445H-S72.445J,S72.446B-S72.446C,S72.446E-S72.446F,S72.446H-S72.446J,S72.451B-S72.451C,S72.451E-S72.451F,S72.451H-S72.451J,S72.452B-S72.452C,S72.452E-S72.452F,S72.452H-S72.452J,S72.453B-S72.453C,S72.453E-S72.453F,S72.453H-S72.453J,S72.454B-S72.454C,S72.454E-S72.454F,S72.454H-S72.454J,S72.455B-S72.455C,S72.455E-S72.455F,S72.455H-S72.455J,S72.456B-S72.456C,S72.456E-S72.456F,S72.456H-S72.456J,S72.461B-S72.461C,S72.461E-S72.461F,S72.461H-S72.461J,S72.462B-S72.462C,S72.462E-S72.462F,S72.462H-S72.462J,S72.463B-S72.463C,S72.463E-S72.463F,S72.463H-S72.463J,S72.464B-S72.464C,S72.464E-S72.464F,S72.464H-S72.464J,S72.465B-S72.465C,S72.465E-S72.465F,S72.465H-S72.465J,S72.466B-S72.466C,S72.466E-S72.466F,S72.466H-S72.466J,S72.491B-S72.491C,S72.491E-S72.491F,S72.491H-S72.491J,S72.492B-S72.492C,S72.492E-S72.492F,S72.492H-S72.492J,S72.499B-S72.499C,S72.499E-S72.499F,S72.499H-S72.499J,S72.8X1B-S72.8X1C,S72.8X1E-S72.8X1F,S72.8X1H-S72.8X1J,S72.8X2B-S72.8X2C,S72.8X2E-S72.8X2F,S72.8X2H-S72.8X2J,S72.8X9B-S72.8X9C,S72.8X9E-S72.8X9F,S72.8X9H-S72.8X9J,S72.90XB-S72.90XC,S72.90XE-S72.90XF,S72.90XH-S72.90XJ,S72.91XB-S72.91XC,S72.91XE-S72.91XF,S72.91XH-S72.91XJ,S72.92XB-S72.92XC,S72.92XE-S72.92XF,S72.92XH-S72.92XJ,S82.001B-S82.001C,S82.001E-S82.001F,S82.001H-S82.001J,S82.002B-S82.002C,S82.002E-S82.002F,S82.002H-S82.002J,S82.009B-S82.009C,S82.009E-S82.009F,S82.009H-S82.009J,S82.011B-S82.011C,S82.011E-S82.011F,S82.011H-S82.011J,S82.012B-S82.012C,S82.012E-S82.012F,S82.012H-S82.012J,S82.013B-S82.013C,S82.013E-S82.013F,S82.013H-S82.013J,S82.014B-S82.014C,S82.014E-S82.014F,S82.014H-S82.014J,S82.015B-S82.015C,S82.015E-S82.015F,S82.015H-S82.015J,S82.016B-S82.016C,S82.016E-S82.016F,S82.016H-S82.016J,S82.021B-S82.021C,S82.021E-S82.021F,S82.021H-S82.021J,S82.022B-S82.022C,S82.022E-S82.022F,S82.022H-S82.022J,S82.023B-S82.023C,S82.023E-S82.023F,S82.023H-S82.023J,S82.024B-S82.024C,S82.024E-S82.024F,S82.024H-S82.024J,S82.025B-S82.025C,S82.025E-S82.025F,S82.025H-S82.025J,S82.026B-S82.026C,S82.026E-S82.026F,S82.026H-S82.026J,S82.031B-S82.031C,S82.031E-S82.031F,S82.031H-S82.031J,S82.032B-S82.032C,S82.0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PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

S82.125J,S82.126B-S82.126C,S82.126E-S82.126F,S82.126H-S82.126J,S82.131B-S82.131C,S82.131E-S82.131F,S82.131H-S82.131J,S82.132B-S82.132C,S82.132E-S82.132F,S82.132H-S82.132J,S82.133B-S82.133C,S82.133E-S82.133F,S82.133H-S82.133J,S82.134B-S82.134C,S82.134E-S82.134F,S82.134H-S82.134J,S82.135B-S82.135C,S82.135E-S82.135F,S82.135H-S82.135J,S82.136B-S82.136C,S82.136E-S82.136F,S82.136H-S82.136J,S82.141B-S82.141C,S82.141E-S82.141F,S82.141H-S82.141J,S82.142B-S82.142C,S82.142E-S82.142F,S82.142H-S82.142J,S82.143B-S82.143C,S82.143E-S82.143F,S82.143H-S82.143J,S82.144B-S82.144C,S82.144E-S82.144F,S82.144H-S82.144J,S82.145B-S82.145C,S82.145E-S82.145F,S82.145H-S82.145J,S82.146B-S82.146C,S82.146E-S82.146F,S82.146H-S82.146J,S82.151B-S82.151C,S82.151E-S82.151F,S82.151H-S82.151J,S82.152B-S82.152C,S82.152E-S82.152F,S82.152H-S82.152J,S82.153B-S82.153C,S82.153E-S82.153F,S82.153H-S82.153J,S82.154B-S82.154C,S82.154E-S82.154F,S82.154H-S82.154J,S82.155B-S82.155C,S82.155E-S82.155F,S82.155H-S82.155J,S82.156B-S82.156C,S82.156E-S82.156F,S82.156H-S82.156J,S82.191B-S82.191C,S82.191E-S82.191F,S82.191H-S82.191J,S82.192B-S82.192C,S82.192E-S82.192F,S82.192H-S82.192J,S82.199B-S82.199C,S82.199E-S82.199F,S82.199H-S82.199J,S82.201B-S82.201C,S82.201E-S82.201F,S82.201H-S82.201J,S82.202B-S82.202C,S82.202E-S82.202F,S82.202H-S82.202J,S82.209B-S82.209C,S82.209E-S82.209F,S82.209H-S82.209J,S82.221B-S82.221C,S82.221E-S82.221F,S82.221H-S82.221J,S82.222B-S82.222C,S82.222E-S82.222F,S82.222H-S82.222J,S82.223B-S82.223C,S82.223E-S82.223F,S82.223H-S82.223J,S82.224B-S82.224C,S82.224E-S82.224F,S82.224H-S82.224J,S82.225B-S82.225C,S82.225E-S82.225F,S82.225H-S82.225J,S82.226B-S82.226C,S82.226E-S82.226F,S82.226H-S82.226J,S82.231B-S82.231C,S82.231E-S82.231F,S82.231H-S82.231J,S82.232B-S82.232C,S82.232E-S82.232F,S82.232H-S82.232J,S82.233B-S82.233C,S82.233E-S82.233F,S82.233H-S82.233J,S82.234B-S82.234C,S82.234E-S82.234F,S82.234H-S82.234J,S82.235B-S82.235C,S82.235E-S82.235F,S82.235H-S82.235J,S82.236B-S82.236C,S82.236E-S82.236F,S82.236H-S82.236J,S82.241B-S82.241C,S82.241E-S82.241F,S82.241H-S82.241J,S82.242B-S82.242C,S82.242E-S82.242F,S82.242H-S82.242J,S82.243B-S82.243C,S82.243E-S82.243F,S82.243H-S82.243J,S82.244B-S82.244C,S82.244E-S82.244F,S82.244H-S82.244J,S82.245B-S82.245C,S82.245E-S82.245F,S82.245H-S82.245J,S82.246B-S82.246C,S82.246E-S82.246F,S82.246H-S82.246J,S82.251B-S82.251C,S82.251E-S82.251F,S82.251H-S82.251J,S82.252B-S82.252C,S82.252E-S82.252F,S82.252H-S82.252J,S82.253B-S82.253C,S82.253E-S82.253F,S82.253H-S82.253J,S82.254B-S82.254C,S82.254E-S82.254F,S82.254H-S82.254J,S82.255B-S82.255C,S82.255E-S82.255F,S82.255H-S82.255J,S82.256B-S82.256C,S82.256E-S82.256F,S82.256H-S82.256J,S82.261B-S82.261C,S82.261E-S82.261F,S82.261H-S82.261J,S82.262B-S82.262C,S82.262E-S82.262F,S82.262H-S82.262J,S82.263B-S82.263C,S82.263E-S82.263F,S82.263H-S82.263J,S82.264B-S82.264C,S82.264E-S82.264F,S82.264H-S82.264J,S82.265B-S82.265C,S82.265E-S82.265F,S82.265H-S82.265J,S82.266B-S82.266C,S82.266E-S82.266F,S82.266H-S82.266J,S82.291B-S82.291C,S82.291E-S82.291F,S82.291H-S82.291J,S82.292B-S82.292C,S82.292E-S82.292F,S82.292H-S82.292J,S82.299B-S82.299C,S82.299E-S82.299F,S82.299H-S82.299J,S82.301B-S82.301C,S82.301E-S82.301F,S82.301H-S82.301J,S82.302B-S82.302C,S82.302E-S82.302F,S82.302H-S82.302J,S82.309B-S82.309C,S82.309E-S82.309F,S82.309H-S82.309J,S82.391B-S82.391C,S82.391E-S82.391F,S82.391H-S82.391J,S82.392B-S82.392C,S82.392E-S82.392F,S82.392H-S82.392J,S82.399B-S82.399C,S82.399E-S82.399F,S82.399H-S82.399J,S82.401B-S82.401C,S82.401E-S82.401F,S82.401H-S82.401J,S82.402B-S82.402C,S82.402E-S82.402F,S82.402H-S82.402J,S82.409B-S82.409C,S82.409E-S82.409F,S82.409H-S82.409J,S82.421B-S82.421C,S82.421E-S82.421F,S82.421H-S82.421J,S82.422B-S82.422C,S82.422E-S82.422F,S82.422H-S82.422J,S82.423B-S82.423C,S82.423E-S82.423F,S82.423H-S82.423J,S82.424B-S82.424C,S82.424E-S82.424F,S82.424H-S82.424J,S82.425B-S82.425C,S82.425E-S82.425F,S82.425H-S82.425J,S82.426B-S82.426C,S82.426E-S82.426F,S82.426H-S82.426J,S82.431B-S82.431C,S82.431E-S82.431F,S82.431H-S82.431J,S82.432B-S82.432C,S82.432E-S82.432F,S82.432H-S82.432J,S82.433B-S82.433C,S82.433E-S82.433F,S82.433H-S82.433J,S82.434B-S82.434C,S82.434E-S82.434F,S82.434H-S82.434J,S82.435B-S82.435C,S82.435E-S82.435F,S82.435H-S82.435J,S82.436B-S82.436C,S82.436E-S82.436F,S82.436H-S82.436J,S82.441B-S82.441C,S82.441E-S82.441F,S82.441H-S82.441J,S82.442B-S82.442C,S82.442E-S82.442F,S82.442H-S82.442J,S82.443B-S82.443C,S82.443E-S82.443F,S82.443H-S82.443J,S82.444B-S82.444C,S82.444E-S82.444F,S82.444H-S82.444J,S82.445B-S82.445C,S82.445E-S82.445F,S82.445H-S82.445J,S82.446B-S82.446C,S82.446E-S82.446F,S82.446H-S82.446J,S82.451B-S82.451C,S82.451E-S82.451F,S82.451H-S82.451J,S82.452B-S82.452C,S82.452E-S82.452F,S82.452H-S82.452J,S82.453B-S82.453C,S82.453E-S82.453F,S82.453H-S82.453J,S82.454B-S82.454C,S82.454E-S82.454F,S82.454H-S82.454J,S82.455B-S82.455C,S82.455E-S82.455F,S82.455H-S82.455J,S82.456B-S82.456C,S82.456E-S82.456F,S82.456H-S82.456J,S82.461B-S82.461C,S82.461E-S82.461F,S82.461H-S82.461J,S82.462B-S82.462C,S82.462E-S82.462F,S82.462H-S82.462J,S82.463B-S82.463C,S82.463E-S82.463F,S82.463H-S82.463J,S82.464B-S82.464C,S82.464E-S82.464F,S82.464H-S82.464J,S82.465B-S82.465C,S82.465E-S82.465F,S82.465H-S82.465J,S82.466B-S82.466C,S82.466E-S82.466F,S82.466H-S82.466J,S82.491B-S82.491C,S82.491E-S82.491F,S82.491H-S82.491J,S82.492B-S82.492C,S82.492E-S82.492F,S82.492H-S82.492J,S82.499B-S82.499C,S82.499E-S82.499F,S82.499H-S82.499J,S82.51XB-S82.51XC,S82.51XE-S82.51XF,S82.51XH-S82.51XJ,S82.52XB-S82.52XC,S82.52XE-S82.52XF,S82.52XH-S82.52XJ,S82.53XB-S82.53XC,S82.53XE-S82.53XF,S82.53XH-S82.53XJ,S82.54XB-S82.54XC,S82.54XE-S82.54XF,S82.54XH-S82.54XJ,S82.55XB-S82.55XC,S82.55XE-S82.55XF,S82.55XH-S82.55XJ,S82.56XB-S82.56XC,S82.56XE-S82.56XF,S82.56XH-S82.56XJ,S82.61XB-S82.61XC,S82.61XE-S82.61XF,S82.61XH-S82.61XJ,S82.62XB-S82.62XC,S82.62XE-S82.62XF,S82.62XH-S82.62XJ,S82.63XB-S82.63XC,S82.63XE-S82.63XF,S82.63XH-S82.63XJ,S82.64XB-S82.64XC,S82.64XE-S82.64XF,S82.64XH-S82.64XJ,S82.65XB-S82.65XC,S82.65XE-S82.65XF,S82.65XH-S82.65XJ,S82.66XB-S82.66XC,S82.66XE-S82.66XF,S82.66XH-S82.66XJ,S82.831B-S82.831C,S82.831E-S82.831F,S82.831H-S82.831J,S82.832B-S82.832C,S82.832E-S82.832F,S82.832H-S82.832J,S82.839B-S82.839C,S82.839E-S82.839F,S82.839H-S82.839J,S82.841B-S82.841C,S82.841E-S82.841F,S82.841H-S82.841J,S82.842B-S82.842C,S82.842E-S82.842F,S82.842H-S82.842J,S82.843B-S82.843C,S82.843E-S82.843F,S82.843H-S82.843J,S82.844B-S82.844C,S82.844E-S82.844F,S82.844H-S82.844J,S82.845B-S82.845C,S82.845E-S82.845F,S82.845H-



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

	S82.845J,S82.846B-S82.846C,S82.846E-S82.846F,S82.846H-S82.846J,S82.851B-S82.851C,S82.851E-S82.851F,S82.851H-S82.851J,S82.852B-S82.852C,S82.852E-S82.852F,S82.852H-S82.852J,S82.853B-S82.853C,S82.853E-S82.853F,S82.853H-S82.853J,S82.854B-S82.854C,S82.854E-S82.854F,S82.854H-S82.854J,S82.855B-S82.855C,S82.855E-S82.855F,S82.855H-S82.855J,S82.856B-S82.856C,S82.856E-S82.856F,S82.856H-S82.856J,S82.861B-S82.861C,S82.861E-S82.861F,S82.861H-S82.861J,S82.862B-S82.862C,S82.862E-S82.862F,S82.862H-S82.862J,S82.863B-S82.863C,S82.863E-S82.863F,S82.863H-S82.863J,S82.864B-S82.864C,S82.864E-S82.864F,S82.864H-S82.864J,S82.865B-S82.865C,S82.865E-S82.865F,S82.865H-S82.865J,S82.866B-S82.866C,S82.866E-S82.866F,S82.866H-S82.866J,S82.871B-S82.871C,S82.871E-S82.871F,S82.871H-S82.871J,S82.872B-S82.872C,S82.872E-S82.872F,S82.872H-S82.872J,S82.873B-S82.873C,S82.873E-S82.873F,S82.873H-S82.873J,S82.874B-S82.874C,S82.874E-S82.874F,S82.874H-S82.874J,S82.875B-S82.875C,S82.875E-S82.875F,S82.875H-S82.875J,S82.876B-S82.876C,S82.876E-S82.876F,S82.876H-S82.876J,S82.891B-S82.891C,S82.891E-S82.891F,S82.891H-S82.891J,S82.892B-S82.892C,S82.892E-S82.892F,S82.892H-S82.892J,S82.899B-S82.899C,S82.899E-S82.899F,S82.899H-S82.899J,S82.90XB-S82.90XC,S82.90XE-S82.90XF,S82.90XH-S82.90XJ,S82.91XB-S82.91XC,S82.91XE-S82.91XF,S82.91XH-S82.91XJ,S82.92XB-S82.92XC,S82.92XE-S82.92XF,S82.92XH-S82.92XJ,S82.92XB-S82.92XC,S82.92XE-S82.92XF,S82.92XH-H
CPT:	11010-11012,11740,11760,12001-12020,12031-12057,20150,20650,20663,20670-20694,21485,21490,22848,23395,23400,23515,23530,23532,23550,23552,23585,23615,23630,23660,23670,23680,24130,24300,24332,24343,24345,24346,24515,24516,24545,24546,24575,24579,24586,24587,24615,24635,24640,24665,24666,24685,25119,25210-25240,25275,25310,25320,25337,25390-25392,25394,25430,25431,25441-25447,25450-25492,25515,25525,25526,25545,25574,25575,25606-25609,25628,25645,25652,25670,25676,25685,25695,25810-25825,26340,26615,26645,26665,26685,26686,26715,26727,26735,26746,26756,26765,26775-26785,26910,27235,27244,27248,27253-27258,27275,27350,27430,27435,27465-27468,27502,27506,27507,27511-27514,27519,27524,27535,27536,27540,27556-27566,27610,27656,27695-27698,27712,27756-27759,27766,27769,27784,27792,27814,27822-27832,27846,27848,28415,28420,28445,28465,28485,28505,28525,28531-28675,28730,29035-29105,29126-29131,29305-29445,29505,29515,29700-29720,29850-29856,29861-29863,29871,29874-29879,29882,29888-29898,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
Line:	133
Condition:	CANCER OF CERVIX (See Guideline Notes 7,11,12,19,64,65)
treatment:	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10:	C53.0-C53.9,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.41
CPT:	32553,38562,38564,38571-38573,38770,44188,44320,44700,49327,49411,49412,53444,55920,57155,57156,57505,57520,57522,57531-57550,57558,58150,58200,58210,58260,58548-58554,58570-58575,58953-



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

- Line: 134**  
Condition: INTERRUPTED AORTIC ARCH (See Guideline Notes 64,65)  
Treatment: TRANSVERSE ARCH GRAFT  
ICD-10: Q25.21-Q25.29,Q25.40-Q25.42,Q25.49  
CPT: 33608,33852,33853,33870,33946-33966,33969,33984-33989,92960-92971,92978-92998,93355,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 135**  
Condition: HODGKIN'S DISEASE (See Guideline Notes 7,11,12,19,64,65)  
Treatment: MEDICAL THERAPY, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C81.00-C81.99,D61.810,G89.3,Z51.0,Z51.12,Z85.71  
CPT: 32553,38100,38120,49203-49205,49220,49411,77014,77261-77295,77300-77307,77321-77370,77385-77387,77401-77427,77469,77470,78811-78816,79403,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537
- Line: 136**  
Condition: TRAUMATIC AMPUTATION OF LEG(S) (COMPLETE)(PARTIAL) WITH AND WITHOUT COMPLICATION (See Guideline Notes 6,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: S78.011A-S78.011D,S78.012A-S78.012D,S78.019A-S78.019D,S78.021A-S78.021D,S78.022A-S78.022D,S78.029A-S78.029D,S78.111A-S78.111D,S78.112A-S78.112D,S78.119A-S78.119D,S78.121A-S78.121D,S78.122A-S78.122D,S78.129A-S78.129D,S78.911A-S78.911D,S78.912A-S78.912D,S78.919A-S78.919D,S78.921A-S78.921D,S78.922A-S78.922D,S78.929A-S78.929D,S88.011A-S88.011D,S88.012A-S88.012D,S88.019A-S88.019D,S88.021A-S88.021D,S88.022A-S88.022D,S88.029A-S88.029D,S88.111A-S88.111D,S88.112A-S88.112D,S88.119A-S88.119D,S88.121A-S88.121D,S88.122A-S88.122D,S88.129A-S88.129D,S88.911A-S88.911D,S88.912A-S88.912D,S88.919A-S88.919D,S88.921A-S88.921D,S88.922A-S88.922D,S88.929A-S88.929D  
CPT: 11010-11012,27290,27295,27590-27598,27880-27886,27889,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 137**  
Condition: OPPORTUNISTIC INFECTIONS IN IMMUNOCOMPROMISED HOSTS; CANDIDIASIS OF STOMA; PERSONS RECEIVING CONTINUOUS ANTIBIOTIC THERAPY (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A02.9,B00.1,B35.0,B35.2-B35.9,B36.1,B37.0,B37.41-B37.49,B37.83,B45.8,B59  
CPT: 11720,11721,17110,17111,92002-92014,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 138**  
Condition: EBSTEIN'S ANOMALY (See Guideline Notes 64,65)  
Treatment: REPAIR SEPTAL DEFECT/VALVULOPLASTY/REPLACEMENT  
ICD-10: Q22.5  
CPT: 33460,33465,33468,33620,33621,33641-33647,33946-33966,33969,33984-33989,75557-75565,75573,93355,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 139**  
Condition: GLAUCOMA, OTHER THAN PRIMARY ANGLE-CLOSURE (See Guideline Notes 64,65)  
Treatment: MEDICAL, SURGICAL AND LASER TREATMENT  
ICD-10: H40.001-H40.029,H40.041-H40.059,H40.10X0-H40.159,H40.30X0-H40.9,H42,Q13.81,Q15.0  
CPT: 65820-65855,66150,66155,66170,66172,66179-66250,66700-66711,66740,66762,66920-66984,67036,67255,67500,76514,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



*PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)*

<b>Line:</b>	<b>140</b>
Condition:	MYASTHENIA GRAVIS (See Guideline Notes 61,64,65)
Treatment:	MEDICAL THERAPY, THYMECTOMY
ICD-10:	G70.00-G70.9,G73.1-G73.3
CPT:	32673,36514,36516,60520-60522,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>141</b>
Condition:	SYSTEMIC LUPUS ERYTHEMATOSUS, OTHER DIFFUSE DISEASES OF CONNECTIVE TISSUE (See Guideline Notes 64,65)
Treatment:	MEDICAL THERAPY
ICD-10:	M32.0,M32.10-M32.9,M35.1,M35.9
CPT:	36514,36516,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>142</b>
Condition:	CONDITIONS INVOLVING THE TEMPERATURE REGULATION OF NEWBORNS (See Guideline Notes 64,65)
Treatment:	MEDICAL THERAPY
ICD-10:	P80.0-P80.9,P81.0-P81.9
CPT:	93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>143</b>
Condition:	PNEUMOTHORAX AND PLEURAL EFFUSION TUBE THORACOSTOMY (See Guideline Notes 64,65)
Treatment:	SURGICAL THERAPY, MEDICAL THERAPY
ICD-10:	J90,J91.0-J91.8,J93.0,J93.11-J93.9,J94.0,J94.2,J95.811-J95.812,J98.2,S27.0XXA-S27.0XXD,S27.1XXA-S27.1XXD,S27.2XXA-S27.2XXD
CPT:	31634,32110,32124,32200-32220,32310,32550,32552,32554-32562,32650-32653,32655,32664,32665,33015-33050,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>144</b>
Condition:	HYPOTHERMIA (See Guideline Notes 64,65)
Treatment:	MEDICAL THERAPY, EXTRACORPOREAL CIRCULATION
ICD-10:	T68.XXA-T68.XXD
CPT:	93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>145</b>
Condition:	ANEMIA OF PREMATUREITY OR TRANSIENT NEONATAL NEUTROPENIA (See Guideline Notes 64,65)
Treatment:	MEDICAL THERAPY
ICD-10:	P61.2,P61.5,P61.8-P61.9
CPT:	93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>146</b>
Condition:	ENTERIC INFECTIONS AND OTHER BACTERIAL FOOD POISONING (See Guideline Notes 64,65,165)
Treatment:	MEDICAL THERAPY
ICD-10:	A00.0-A00.9,A02.0,A02.8-A02.9,A03.0-A03.9,A04.0-A04.6,A04.71-A04.8,A05.0,A05.2-A05.9,A08.0,A08.11-A08.8,A09
CPT:	44705,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0455,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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**Line: 147**  
Condition: GLYCOGENOSIS (See Guideline Notes 64,65,67)  
Treatment: MEDICAL THERAPY  
ICD-10: E74.00-E74.09  
CPT: 93792,93793,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9357

**Line: 148**  
Condition: ACQUIRED HEMOLYTIC ANEMIAS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: D59.0-D59.9,D62  
CPT: 36514,36516,90935,90937,90945,90947,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 149**  
Condition: FEEDING AND EATING DISORDERS OF INFANCY OR CHILDHOOD (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F50.82-F50.89,F98.21-F98.3  
CPT: 90846,90849,90853,90882,90887,92526,93792,93793,97802-97804,98966-98969,99051,99060,99201-99239,99304-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017,H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005

**Line: 150**  
Condition: CERVICAL VERTEBRAL DISLOCATIONS/FRACTURES, OPEN OR CLOSED; OTHER VERTEBRAL DISLOCATIONS/FRACTURES, OPEN OR UNSTABLE; SPINAL CORD INJURIES WITH OR WITHOUT EVIDENCE OF VERTEBRAL INJURY (See Guideline Notes 6,64,65,100,136)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: M43.3-M43.4,M43.5X2-M43.5X3,M48.40XA-M48.40XG,M48.41XA-M48.41XG,M48.42XA-M48.42XG,M48.43XA-M48.43XG,M48.50XA-M48.50XG,M48.51XA-M48.51XG,M48.52XA-M48.52XG,M48.53XA-M48.53XG,M80.08XA-M80.08XG,M80.88XA-M80.88XG,M84.58XA,M84.68XA,S12.000A-S12.000G,S12.001A-S12.001G,S12.01XA-S12.01XG,S12.02XA-S12.02XG,S12.030A-S12.030G,S12.031A-S12.031G,S12.040A-S12.040G,S12.041A-S12.041G,S12.090A-S12.090G,S12.091A-S12.091G,S12.100A-S12.100G,S12.101A-S12.101G,S12.110A-S12.110G,S12.111A-S12.111G,S12.112A-S12.112G,S12.120A-S12.120G,S12.121A-S12.121G,S12.130A-S12.130G,S12.131A-S12.131G,S12.14XA-S12.14XG,S12.150A-S12.150G,S12.151A-S12.151G,S12.190A-S12.190G,S12.191A-S12.191G,S12.200A-S12.200G,S12.201A-S12.201G,S12.230A-S12.230G,S12.231A-S12.231G,S12.24XA-S12.24XG,S12.250A-S12.250G,S12.251A-S12.251G,S12.290A-S12.290G,S12.291A-S12.291G,S12.300A-S12.300G,S12.301A-S12.301G,S12.330A-S12.330G,S12.331A-S12.331G,S12.34XA-S12.34XG,S12.350A-S12.350G,S12.351A-S12.351G,S12.390A-S12.390G,S12.391A-S12.391G,S12.400A-S12.400G,S12.401A-S12.401G,S12.430A-S12.430G,S12.431A-S12.431G,S12.44XA-S12.44XG,S12.450A-S12.450G,S12.451A-S12.451G,S12.490A-S12.490G,S12.491A-S12.491G,S12.500A-S12.500G,S12.501A-S12.501G,S12.530A-S12.530G,S12.531A-S12.531G,S12.54XA-S12.54XG,S12.550A-S12.550G,S12.551A-S12.551G,S12.590A-S12.590G,S12.591A-S12.591G,S12.600A-S12.600G,S12.601A-S12.601G,S12.630A-S12.630G,S12.631A-S12.631G,S12.64XA-S12.64XG,S12.650A-S12.650G,S12.651A-S12.651G,S12.690A-S12.690G,S12.691A-S12.691G,S12.9XXA-S12.9XXD,S13.100A-S13.100D,S13.101A-S13.101D,S13.110A-S13.110D,S13.111A-S13.111D,S13.120A-S13.120D,S13.121A-S13.121D,S13.130A-S13.130D,S13.131A-S13.131D,S13.140A-S13.140D,S13.141A-S13.141D,S13.150A-S13.150D,S13.151A-S13.151D,S13.160A-S13.160D,S13.161A-S13.161D,S13.170A-S13.170D,S13.171A-S13.171D,S13.180A-S13.180D,S13.181A-S13.181D,S14.0XXA-S14.0XXD,S14.101A-S14.101D,S14.102A-S14.102D,S14.103A-S14.103D,S14.104A-S14.104D,S14.105A-S14.105D,S14.106A-S14.106D,S14.107A-S14.107D,S14.108A-S14.108D,S14.109A-S14.109D,S14.111A-S14.111D,S14.112A-S14.112D,S14.113A-S14.113D,S14.114A-S14.114D,S14.115A-S14.115D,S14.116A-S14.116D,S14.117A-S14.117D,S14.118A-S14.118D,S14.119A-S14.119D,S14.121A-S14.121D,S14.122A-S14.122D,S14.123A-S14.123D,S14.124A-S14.124D,S14.125A-S14.125D,S14.126A-S14.126D,S14.127A-S14.127D,S14.128A-S14.128D,S14.129A-S14.129D,S14.131A-S14.131D,S14.132A-S14.132D,S14.133A-S14.133D,S14.134A-S14.134D,S14.135A-S14.135D,S14.136A-S14.136D,S14.137A-S14.137D,S14.138A-S14.138D,S14.139A-S14.139D,S14.141A-S14.141D,S14.142A-S14.142D,S14.143A-S14.143D,S14.144A-S14.144D,S14.145A-S14.145D,S14.146A-S14.146D,S14.147A-S14.147D,S14.148A-S14.148D,S14.149A-S14.149D,S14.151A-S14.151D,S14.152A-S14.152D,S14.153A-S14.153D,S14.154A-S14.154D,S14.155A-S14.155D,S14.156A-S14.156D,S14.157A-S14.157D,S14.158A-S14.158D,S14.159A-S14.159D,S22.000B-S22.000G,S22.001B-S22.001G,S22.002B-S22.002G,S22.008B-S22.008G,S22.009B-S22.009G,S22.010B-S22.010G,S22.011B-S22.011G,S22.012B-S22.012G,S22.018B-S22.018G,S22.019B-S22.019G,S22.020B-S22.020G,S22.021B-S22.021G,S22.022B-S22.022G,S22.028B-S22.028G,S22.029B-S22.029G,S22.030B-S22.030G,S22.031B-S22.031G,S22.032B-S22.032G,S22.038B-S22.038G,S22.039B-S22.039G,S22.040B-S22.040G,S22.041B-S22.041G,S22.042B-S22.042G,S22.048B-S22.048G,S22.049B-S22.049G,S22.050B-S22.050G,S22.051B-S22.051G,S22.052B-S22.052G,S22.058B-S22.058G,S22.059B-S22.059G,S22.060B-S22.060G,S22.061B-S22.061G,S22.062B-S22.062G,S22.068B-S22.068G,S22.069B-S22.069G



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S22.069G,S22.070B-S22.070G,S22.071B-S22.071G,S22.072B-S22.072G,S22.078B-S22.078G,S22.079B-S22.079G,S22.080B-S22.080G,S22.081B-S22.081G,S22.082B-S22.082G,S22.088B-S22.088G,S22.089B-S22.089G,S24.0XXA-S24.0XXD,S24.101A-S24.101D,S24.102A-S24.102D,S24.103A-S24.103D,S24.104A-S24.104D,S24.109A-S24.109D,S24.111A-S24.111D,S24.112A-S24.112D,S24.113A-S24.113D,S24.114A-S24.114D,S24.119A-S24.119D,S24.131A-S24.131D,S24.132A-S24.132D,S24.133A-S24.133D,S24.134A-S24.134D,S24.139A-S24.139D,S24.141A-S24.141D,S24.142A-S24.142D,S24.143A-S24.143D,S24.144A-S24.144D,S24.149A-S24.149D,S24.151A-S24.151D,S24.152A-S24.152D,S24.153A-S24.153D,S24.154A-S24.154D,S24.159A-S24.159D,S32.000B-S32.000G,S32.001B-S32.001G,S32.002A-S32.002G,S32.008B-S32.008G,S32.009B-S32.009G,S32.010B-S32.010G,S32.011B-S32.011G,S32.012A-S32.012G,S32.018B-S32.018G,S32.019B-S32.019G,S32.020B-S32.020G,S32.021B-S32.021G,S32.022A-S32.022G,S32.028B-S32.028G,S32.029B-S32.029G,S32.030B-S32.030G,S32.031B-S32.031G,S32.032A-S32.032G,S32.038B-S32.038G,S32.039B-S32.039G,S32.040B-S32.040G,S32.041B-S32.041G,S32.042A-S32.042G,S32.048B-S32.048G,S32.049B-S32.049G,S32.050B-S32.050G,S32.051B-S32.051G,S32.052A-S32.052G,S32.058B-S32.058G,S32.059B-S32.059G,S32.10XB,S32.110B,S32.111B,S32.112B,S32.119B,S32.120B,S32.121B,S32.122B,S32.129B,S32.130B,S32.131B,S32.132B,S32.139B,S32.14XB,S32.15XB,S32.16XB,S32.17XB,S32.19XB,S34.01XA-S34.01XD,S34.02XA-S34.02XD,S34.101A-S34.101D,S34.102A-S34.102D,S34.103A-S34.103D,S34.104A-S34.104D,S34.105A-S34.105D,S34.109A-S34.109D,S34.111A-S34.111D,S34.112A-S34.112D,S34.113A-S34.113D,S34.114A-S34.114D,S34.115A-S34.115D,S34.119A-S34.119D,S34.121A-S34.121D,S34.122A-S34.122D,S34.123A-S34.123D,S34.124A-S34.124D,S34.125A-S34.125D,S34.129A-S34.129D,S34.131A-S34.131D,S34.132A-S34.132D,S34.139A-S34.139D,Z47.2

CPT: 11010-11012,20660,20661,20665,20690-20694,20930-20938,22100-22116,22310-22505,22532-22819,22840-22855,22859,27202-27216,29015,29040,29710,29720,63001-63173,63295,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 151**  
Condition: DISORDERS OF MINERAL METABOLISM, OTHER THAN CALCIUM (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: E83.00-E83.10,E83.110-E83.19,E83.30-E83.49,E83.89  
CPT: 93792,93793,97802-97804,98966-98969,99051,99060,99070,99078,99184,99195,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9355

**Line: 152**  
Condition: NON-PULMONARY TUBERCULOSIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A17.83,A17.9,A18.01-A18.89,A19.0-A19.9  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 153**  
Condition: PYOGENIC ARTHRITIS (See Guideline Notes 6,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: A01.04,A02.23,A39.83,M00.00,M00.011-M00.9,M01.X0,M01.X11-M01.X9  
CPT: 20600-20611,23040,23044,24000,24006,24101,24102,25040,25101-25109,26070-26080,27030,27310,27610,28022,28024,29819,29821-29823,29825,29843,29848,29861-29863,29871,29894,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 154**  
Condition: VASCULAR INSUFFICIENCY OF INTESTINE (See Guideline Notes 64,65)  
Treatment: SURGICAL TREATMENT  
ICD-10: K55.011-K55.1,K55.8-K55.9,Z46.59  
CPT: 34151,34421,34451,44120-44125,44130,44139-44160,44202-44213,44310,44701,49442,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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- Line: 155**  
Condition: HERPES ZOSTER; HERPES SIMPLEX AND WITH NEUROLOGICAL AND OPHTHALMOLOGICAL COMPLICATIONS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: B00.2-B00.4,B00.50-B00.89,B02.0-B02.1,B02.21-B02.9,B10.01-B10.09,G93.7  
CPT: 65430,69676,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 156**  
Condition: ACROMEGALY AND GIGANTISM (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: E22.0  
CPT: 32553,48140,48155,49411,60200-60240,60270,60271,60512,60600-60650,61548,62100,79005-79445,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 157**  
Condition: CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS (See Guideline Notes 7,11,12,19,23,64,65,148)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C17.0-C17.9,C18.0-C18.9,C19-C20,C21.0-C21.8,C49.A0,C49.A3-C49.A9,C7A.010-C7A.029,D01.0-D01.3,D01.40-D01.49,D37.2-D37.5,D37.8,D61.810,G89.3,K62.82-K62.89,K63.89,Z46.59,Z51.0,Z51.11-Z51.12,Z85.038,Z85.048  
CPT: 32553,38747,43245,44120-44125,44139-44160,44187,44188,44204-44227,44300-44346,44379,44381,44384,44391-44402,44404,44405,44620-44626,44701,45110-45113,45119,45123,45126,45136,45171-45190,45303,45308-45320,45327,45333-45335,45338-45347,45381-45389,45395,45397,45402,45505,45550,46604,46900-46924,49203-49205,49411,49442,57156,58150,77014,77261-77295,77300-77370,77385-77387,77401-77417,77424-77432,77469,77470,77761-77763,77770-77790,78811-78816,79005-79445,81275,81288,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537
- Line: 158**  
Condition: NON-HODGKIN'S LYMPHOMAS (See Guideline Notes 7,11,12,19,64,65,115)  
Treatment: MEDICAL THERAPY, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C82.00-C82.99,C83.00-C83.99,C84.00-C84.99,C85.10-C85.99,C86.0-C86.6,C88.4-C88.8,C96.0,C96.20-C96.9,D46.20-D46.C,D46.Z-D46.9,D47.01-D47.1,D47.3,D47.Z1-D47.Z9,D61.810,G89.3,Z51.0,Z51.12  
CPT: 32553,36522,38100,38120,38542,38720,49411,77014,77261-77295,77300-77307,77321-77370,77385-77387,77401-77431,77469,77470,78811-78816,79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9355,S9537
- Line: 159**  
Condition: TOXIC EPIDERMAL NECROLYSIS AND STAPHYLOCOCCAL SCALDED SKIN SYNDROME; STEVENS-JOHNSON SYNDROME; ERYTHEMA MULTIFORME MAJOR; ECZEMA HERPETICUM (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: B00.0,L00,L12.30-L12.35,L51.1-L51.3  
CPT: 36514,36516,65778-65782,68371,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 160**  
Condition: TRAUMATIC AMPUTATION OF ARM(S), HAND(S), THUMB(S), AND FINGER(S) (COMPLETE)(PARTIAL) WITH AND WITHOUT COMPLICATION (See Guideline Notes 6,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: S48.011A-S48.011D,S48.012A-S48.012D,S48.019A-S48.019D,S48.021A-S48.021D,S48.022A-S48.022D,S48.029A-S48.029D,S48.111A-S48.111D,S48.112A-S48.112D,S48.119A-S48.119D,S48.121A-S48.121D,S48.122A-S48.122D,S48.129A-S48.129D,S48.911A-S48.911D,S48.912A-S48.912D,S48.919A-S48.919D,S48.921A-S48.921D,S48.922A-S48.922D,S48.929A-S48.929D,S58.011A-S58.011D,S58.012A-S58.012D,S58.019A-S58.019D,S58.021A-S58.021D,S58.022A-S58.022D,S58.029A-S58.029D,S58.111A-S58.111D,S58.112A-S58.112D,S58.119A-S58.119D,S58.121A-S58.121D,S58.122A-S58.122D,S58.129A-S58.129D,S58.911A-S58.911D,S58.912A-S58.912D,S58.919A-S58.919D,S58.921A-S58.921D,S58.922A-S58.922D,S58.929A-S58.929D,S68.011A-S68.011D,S68.012A-S68.012D,S68.019A-S68.019D,S68.021A-S68.021D,



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- S68.022A-S68.022D,S68.029A-S68.029D,S68.110A-S68.110D,S68.111A-S68.111D,S68.112A-S68.112D,  
S68.113A-S68.113D,S68.114A-S68.114D,S68.115A-S68.115D,S68.116A-S68.116D,S68.117A-S68.117D,  
S68.118A-S68.118D,S68.119A-S68.119D,S68.120A-S68.120D,S68.121A-S68.121D,S68.122A-S68.122D,  
S68.123A-S68.123D,S68.124A-S68.124D,S68.125A-S68.125D,S68.126A-S68.126D,S68.127A-S68.127D,  
S68.128A-S68.128D,S68.129A-S68.129D,S68.411A-S68.411D,S68.412A-S68.412D,S68.419A-S68.419D,  
S68.421A-S68.421D,S68.422A-S68.422D,S68.429A-S68.429D,S68.511A-S68.511D,S68.512A-S68.512D,  
S68.519A-S68.519D,S68.521A-S68.521D,S68.522A-S68.522D,S68.529A-S68.529D,S68.610A-S68.610D,  
S68.611A-S68.611D,S68.612A-S68.612D,S68.613A-S68.613D,S68.614A-S68.614D,S68.615A-S68.615D,  
S68.616A-S68.616D,S68.617A-S68.617D,S68.618A-S68.618D,S68.619A-S68.619D,S68.620A-S68.620D,  
S68.621A-S68.621D,S68.622A-S68.622D,S68.623A-S68.623D,S68.624A-S68.624D,S68.625A-S68.625D,  
S68.626A-S68.626D,S68.627A-S68.627D,S68.628A-S68.628D,S68.629A-S68.629D,S68.711A-S68.711D,  
S68.712A-S68.712D,S68.719A-S68.719D,S68.721A-S68.721D,S68.722A-S68.722D,S68.729A-S68.729D
- CPT: 11000,11001,11010-11047,20802-20838,20910,20912,20972,20973,23900-23921,24900-24940,25900-25909,  
26350-26356,26410-26418,26551-26556,26910-26952,64831,64832,93792,93793,96150-96155,97012,97110-  
97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-  
99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
- HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,  
G0513,G0514
- Line: 161**  
Condition: GRANULOCYTE DISORDERS (See Guideline Notes 7,11,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: D70.0-D70.8,D71.0,D72.0,D72.89,D76.1-D76.3  
CPT: 79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96440,96450,96542,96549,96570,96571,  
98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-  
99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,  
S9537
- Line: 162**  
Condition: BILIARY ATRESIA  
Treatment: LIVER TRANSPLANT  
ICD-10: Q44.2-Q44.3,T86.40-T86.49,Z48.23,Z52.6  
CPT: 47133-47147,86825-86835,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-  
99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 163**  
Condition: NON-HODGKIN'S LYMPHOMAS (See Guideline Notes 7,11,12,14,19)  
Treatment: BONE MARROW TRANSPLANT  
ICD-10: C82.00-C82.99,C83.00-C83.99,C84.00-C84.99,C85.10-C85.99,C86.0-C86.6,C88.4,C96.4,C96.A-C96.9,D61.810,  
T86.01-T86.09,T86.5,Z48.290,Z52.000-Z52.098,Z52.3  
CPT: 36680,38204-38215,38230-38243,78811-78816,86825-86835,90284,93792,93793,96377,96405,96406,96420-  
96440,96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-  
99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,  
G0514,S2142,S2150,S9537
- Line: 164**  
Condition: CARCINOMA IN SITU OF UPPER AIRWAY, INCLUDING ORAL CAVITY (See Guideline Notes 64,65)  
Treatment: INCISION/EXCISION, MEDICAL THERAPY  
ICD-10: D00.00-D00.08,K13.29  
CPT: 40500-40530,40810-40816,40819,40820,41000-41018,41110-41510,41520,93792,93793,98966-98969,99051,  
99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,  
99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 165**  
Condition: PREVENTIVE FOOT CARE IN HIGH RISK PATIENTS  
Treatment: MEDICAL AND SURGICAL TREATMENT OF TOENAILS AND HYPERKERATOSES OF FOOT  
ICD-10: E08.40-E08.42,E08.51-E08.52,E08.621,E09.40-E09.42,E09.51-E09.52,E09.621,E10.40-E10.42,E10.51-E10.52,  
E10.621,E11.40-E11.42,E11.49-E11.59,E11.621,E11.628,E13.40-E13.42,E13.44,E13.51-E13.52,E13.621,G60.0-  
G60.8,G62.1,I70.201-I70.299,Z86.31  
CPT: 11719-11732,11750,28011,28100-28108,28120-28124,28200-28210,93792,93793,98966-98969,99051,99060,  
99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-  
99498,99605-99607  
HCPCS: G0245-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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- Line: 166**  
Condition: ANAL, RECTAL AND COLONIC POLYPS  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: D12.0-D12.9,D3A.020-D3A.029,K51.40,K62.0-K62.1,K63.5,Z86.010  
CPT: 44110,44140-44160,44204-44213,44391-44401,44404,44620-44626,45113-45116,45171,45172,45308-45320,45333-45335,45338,45346,45381-45385,45388,46610-46612,46615,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 167**  
Condition: GONOCOCCAL AND CHLAMYDIAL INFECTIONS OF THE EYE; NEONATAL CONJUNCTIVITIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A54.30-A54.39,A74.0,P37.5,P39.1  
CPT: 92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 168**  
Condition: COMPLICATED HERNIAS; UNCOMPLICATED INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER; PERSISTENT HYDROCELE (See Guideline Notes 24,63,64,65,149)  
Treatment: REPAIR  
ICD-10: K40.00-K40.91,K41.00-K41.11,K41.30-K41.41,K42.0-K42.1,K43.0-K43.1,K43.3-K43.4,K43.6-K43.7,K44.0-K44.1,K45.0-K45.1,K46.0-K46.1,N43.0,N43.2-N43.3,P83.5  
CPT: 39503-39541,39560,39561,43281-43283,44050,44120,44346,49491-49572,49582,49587,49590,49650-49659,55040-55060,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 169**  
Condition: NON-DIABETIC HYPOGLYCEMIC COMA (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: E15  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 170**  
Condition: ACUTE MASTOIDITIS (See Guideline Notes 64,65)  
Treatment: MASTOIDECTOMY, MEDICAL THERAPY  
ICD-10: H70.001-H70.099,H70.201-H70.229,H75.00-H75.03  
CPT: 69420,69421,69433,69436,69501-69540,69601-69646,69670,69700,69801,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 171**  
Condition: AMEBIASIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A06.0-A06.3,A06.7,A06.81-A06.9,A07.0-A07.1,A07.8,B60.10-B60.11,B60.19-B60.8  
CPT: 92002-92014,92018-92060,92081-92136,92225,92226,92230,92235,92242-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 172**  
Condition: HYPERTENSIVE HEART AND RENAL DISEASE (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: I13.0,I13.10-I13.2,I15.0-I15.1,N26.2  
CPT: 92960-92971,92978-92998,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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JANUARY 1, 2018 (REVISED)**

**Line: 173**  
Condition: POSTTRAUMATIC STRESS DISORDER (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F43.10-F43.12  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99281-99285,99304-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005

**Line: 174**  
Condition: GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS (See Guideline Note 19)  
Treatment: SINGLE FOCAL SURGERY  
ICD-10: G40.001-G40.219,G40.309-G40.319,Z45.42-Z45.49,Z46.2  
CPT: 61531-61537,61540-61543,61566,61567,61720,61735,61760,61850-61888,64568-64570,78608,78609,78811,78814,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 175**  
Condition: POLYARTERITIS NODOSA AND ALLIED CONDITIONS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: I67.7,M30.0,M30.2,M30.8,M31.1,M31.7,M35.2  
CPT: 36514,36516,92002-92014,92235,92242,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 176**  
Condition: COMMON VENTRICLE (See Guideline Notes 64,65)  
Treatment: TOTAL REPAIR  
ICD-10: Q20.4,Q20.8  
CPT: 33600,33602,33608,33610,33615,33617,33620-33622,33692,33694,33735-33750,33764-33768,33924,33946-33966,33969,33984-33989,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 177**  
Condition: DISORDERS OF AMINO-ACID TRANSPORT AND METABOLISM (NON PKU); HEREDITARY FRUCTOSE INTOLERANCE (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: E70.20-E70.29,E70.320-E70.39,E70.5-E70.9,E71.0,E71.110-E71.2,E72.00,E72.02-E72.52,E72.59-E72.9,E73.0,E74.12-E74.19,E74.4-E74.8  
CPT: 93792,93793,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 178**  
Condition: INTRACEREBRAL HEMORRHAGE (See Guideline Notes 6,64,65,90)  
Treatment: MEDICAL THERAPY  
ICD-10: I61.0-I61.9  
CPT: 92507,92508,92521-92526,92607-92609,92633,93792,93793,96150-96155,97012,97110-97127,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513-G0515,S9152



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

<b>Line:</b>	<b>179</b>
Condition:	ACUTE LEUKEMIA, MYELODYSPLASTIC SYNDROME (See Guideline Notes 7,11,12,14)
Treatment:	BONE MARROW TRANSPLANT
ICD-10:	C88.8,C90.10-C90.12,C91.00-C91.02,C95.00-C95.02,D46.0-D46.1,D46.20-D46.9,D47.1,D47.3,D61.810,Z48.290,Z52.000-Z52.098,Z52.3
CPT:	36680,38204-38215,38230-38243,86828-86835,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S2142,S2150,S9537
<b>Line:</b>	<b>180</b>
Condition:	URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER (See Guideline Notes 64,65)
Treatment:	MEDICAL AND SURGICAL TREATMENT
ICD-10:	N11.1,N13.0-N13.2,N13.30-N13.5,N28.82
CPT:	50070,50075,50100,50220,50382-50389,50395,50400,50405,50432-50435,50544,50553,50572,50575,50576,50605,50693-50700,50706-50740,50760,50780-50785,50840-50900,50940,50948,50953,50970,50972,51535,52276,52290,52301,52310,52315,52327-52346,52352-52354,52356,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>181</b>
Condition:	CONDITIONS INVOLVING EXPOSURE TO NATURAL ELEMENTS (E.G., LIGHTNING STRIKE, HEATSTROKE) (See Guideline Notes 64,65)
Treatment:	MEDICAL THERAPY, BURN TREATMENT
ICD-10:	L55.2,T33.011A-T33.011D,T33.012A-T33.012D,T33.019A-T33.019D,T33.02XA-T33.02XD,T33.09XA-T33.09XD,T33.1XXA-T33.1XXD,T33.2XXA-T33.2XXD,T33.3XXA-T33.3XXD,T33.40XA-T33.40XD,T33.41XA-T33.41XD,T33.42XA-T33.42XD,T33.511A-T33.511D,T33.512A-T33.512D,T33.519A-T33.519D,T33.521A-T33.521D,T33.522A-T33.522D,T33.529A-T33.529D,T33.531A-T33.531D,T33.532A-T33.532D,T33.539A-T33.539D,T33.60XA-T33.60XD,T33.61XA-T33.61XD,T33.62XA-T33.62XD,T33.70XA-T33.70XD,T33.71XA-T33.71XD,T33.72XA-T33.72XD,T33.811A-T33.811D,T33.812A-T33.812D,T33.819A-T33.819D,T33.821A-T33.821D,T33.822A-T33.822D,T33.829A-T33.829D,T33.831A-T33.831D,T33.832A-T33.832D,T33.839A-T33.839D,T33.90XA-T33.90XD,T33.99XA-T33.99XD,T34.011A-T34.011D,T34.012A-T34.012D,T34.019A-T34.019D,T34.02XA-T34.02XD,T34.09XA-T34.09XD,T34.1XXA-T34.1XXD,T34.2XXA-T34.2XXD,T34.3XXA-T34.3XXD,T34.40XA-T34.40XD,T34.41XA-T34.41XD,T34.42XA-T34.42XD,T34.511A-T34.511D,T34.512A-T34.512D,T34.519A-T34.519D,T34.521A-T34.521D,T34.522A-T34.522D,T34.529A-T34.529D,T34.531A-T34.531D,T34.532A-T34.532D,T34.539A-T34.539D,T34.60XA-T34.60XD,T34.61XA-T34.61XD,T34.62XA-T34.62XD,T34.70XA-T34.70XD,T34.71XA-T34.71XD,T34.72XA-T34.72XD,T34.811A-T34.811D,T34.812A-T34.812D,T34.819A-T34.819D,T34.821A-T34.821D,T34.822A-T34.822D,T34.829A-T34.829D,T34.831A-T34.831D,T34.832A-T34.832D,T34.839A-T34.839D,T34.90XA-T34.90XD,T34.99XA-T34.99XD,T67.0XXA-T67.0XXD,T67.1XXA-T67.1XXD,T67.2XXA-T67.2XXD,T67.3XXA-T67.3XXD,T67.4XXA-T67.4XXD,T67.5XXA-T67.5XXD,T67.6XXA-T67.6XXD,T67.7XXA-T67.7XXD,T67.8XXA-T67.8XXD,T67.9XXA-T67.9XXD,T69.011A-T69.011D,T69.012A-T69.012D,T69.019A-T69.019D,T69.021A-T69.021D,T69.022A-T69.022D,T69.029A-T69.029D,T69.1XXA-T69.1XXD,T69.8XXA-T69.8XXD,T69.9XXA-T69.9XXD,T70.20XA-T70.20XD,T70.29XA-T70.29XD,T70.4XXA-T70.4XXD,T70.8XXA-T70.8XXD,T71.20XA-T71.20XD,T71.21XA-T71.21XD,T71.221A-T71.221D,T71.222A-T71.222D,T71.223A-T71.223D,T71.224A-T71.224D,T71.231A-T71.231D,T71.232A-T71.232D,T71.233A-T71.233D,T71.234A-T71.234D,T71.29XA-T71.29XD,T71.9XXA-T71.9XXD,T73.2XXA-T73.2XXD,T73.8XXA-T73.8XXD,T73.9XXA-T73.9XXD,T75.00XA-T75.00XD,T75.01XA-T75.01XD,T75.09XA-T75.09XD,T75.1XXA-T75.1XXD,T75.20XA-T75.20XD,T75.21XA-T75.21XD,T75.22XA-T75.22XD,T75.23XA-T75.23XD,T75.29XA-T75.29XD,T75.4XXA-T75.4XXD,T75.81XA-T75.81XD,T75.82XA-T75.82XD,T75.89XA-T75.89XD,T78.8XXA-T78.8XXD,T88.51XA-T88.51XD
CPT:	11000,11960-11971,15002-15005,15271-15278,16000-16036,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>182</b>
Condition:	SEPTICEMIA (See Guideline Notes 64,65)
Treatment:	MEDICAL THERAPY
ICD-10:	A01.00,A01.02,A01.09-A01.4,A02.1,A20.7,A22.7,A26.7,A32.7,A39.1-A39.2,A39.4,A39.89,A40.0-A40.9,A41.01-A41.9,A42.7,A48.3,A54.86,A77.0,A96.0-A96.9,A98.3-A98.8,A99,B33.4,B37.7,P36.0,P36.10-P36.9,P39.2,R65.10-R65.21,R78.81,T81.12XA-T81.12XD
CPT:	33946-33966,33969,33984-33989,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

**Line: 183**  
Condition: FRACTURE OF PELVIS, OPEN AND CLOSED (See Guideline Notes 6,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: M84.350A-M84.350G,M84.454A-M84.454G,M84.550A-M84.550G,M84.650A-M84.650G,M91.0,M91.80-M91.92,  
S32.301A-S32.301G,S32.302A-S32.302G,S32.309A-S32.309G,S32.311A-S32.311G,S32.312A-S32.312G,  
S32.313A-S32.313G,S32.314A-S32.314G,S32.315A-S32.315G,S32.316A-S32.316G,S32.391A-S32.391G,  
S32.392A-S32.392G,S32.399A-S32.399G,S32.401A-S32.401G,S32.402A-S32.402G,S32.409A-S32.409G,  
S32.411A-S32.411G,S32.412A-S32.412G,S32.413A-S32.413G,S32.414A-S32.414G,S32.415A-S32.415G,  
S32.416A-S32.416G,S32.421A-S32.421G,S32.422A-S32.422G,S32.423A-S32.423G,S32.424A-S32.424G,  
S32.425A-S32.425G,S32.426A-S32.426G,S32.431A-S32.431G,S32.432A-S32.432G,S32.433A-S32.433G,  
S32.434A-S32.434G,S32.435A-S32.435G,S32.436A-S32.436G,S32.441A-S32.441G,S32.442A-S32.442G,  
S32.443A-S32.443G,S32.444A-S32.444G,S32.445A-S32.445G,S32.446A-S32.446B,S32.446G,S32.451A-  
S32.451G,S32.452A-S32.452G,S32.453A-S32.453G,S32.454A-S32.454G,S32.455A-S32.455G,S32.456A-  
S32.456G,S32.461A-S32.461G,S32.462A-S32.462G,S32.463A-S32.463G,S32.464A-S32.464G,S32.465A-  
S32.465G,S32.466A-S32.466G,S32.471A-S32.471G,S32.472A-S32.472G,S32.473A-S32.473G,S32.474A-  
S32.474G,S32.475A-S32.475G,S32.476A-S32.476G,S32.481A-S32.481G,S32.482A-S32.482G,S32.483A-  
S32.483G,S32.484A-S32.484G,S32.485A-S32.485G,S32.486A-S32.486G,S32.491A-S32.491G,S32.492A-  
S32.492G,S32.499A-S32.499G,S32.501A-S32.501G,S32.502A-S32.502G,S32.509A-S32.509G,S32.511A-  
S32.511G,S32.512A-S32.512G,S32.519A-S32.519G,S32.591A-S32.591G,S32.592A-S32.592G,S32.599A-  
S32.599G,S32.601A-S32.601G,S32.602A-S32.602G,S32.609A-S32.609G,S32.611A-S32.611G,S32.612A-  
S32.612G,S32.613A-S32.613G,S32.614A-S32.614G,S32.615A-S32.615G,S32.616A-S32.616G,S32.691A-  
S32.691G,S32.692A-S32.692G,S32.699A-S32.699G,S32.810A-S32.810G,S32.811A-S32.811G,S32.82XA-  
S32.82XK,S32.89XA-S32.89XG,S32.9XXA-S32.9XXG,S33.4XXA-S33.4XXD,Z47.2  
CPT: 11010-11012,20690-20694,27033,27197,27198,27215-27228,27279-27282,29035-29046,29305,29325,29710,  
29720,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,  
99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,  
99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0412-G0415,G0425-G0427,G0463-G0467,G0490,  
G0508-G0511,G0513,G0514

**Line: 184**  
Condition: ACUTE OSTEOMYELITIS (See Guideline Notes 6,64,65,148)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: A01.05,A02.24,B37.89,M86.00,M86.011-M86.29,M86.9  
CPT: 20150,20955-20973,21025,21026,21510,22010,22015,23035,23105,23130,23170-23184,23405,23406,23900-  
23921,23935,24134-24147,24420,24900-24930,25035,25085,25119,25145-25151,25210-25240,25900-25909,  
25920-25931,26034,26910-26952,26992,27025,27054,27070,27071,27290,27295,27303,27360,27590-27598,  
27607,27705-27709,27880-27889,28005,28120-28124,28800-28825,93792,93793,96150-96155,97012,97110-  
97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-  
99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,  
G0513,G0514

**Line: 185**  
Condition: DIVERTICULITIS OF COLON (See Guideline Notes 64,65)  
Treatment: COLON RESECTION, MEDICAL THERAPY  
ICD-10: K57.10,K57.12-K57.13,K57.30,K57.32-K57.33,K57.50,K57.52-K57.53,K57.90,K57.92-K57.93  
CPT: 33238,44005,44139-44147,44160,44188,44204-44208,44213,44227,44320,44391,44404,44620-44626,44701,  
45308-45320,45334,45335,45381,45382,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,  
99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-  
99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 186**  
Condition: RHEUMATIC MULTIPLE VALVULAR DISEASE (See Guideline Notes 64,65)  
Treatment: SURGICAL TREATMENT  
ICD-10: I07.0-I07.9,I08.0-I08.9,I09.1,I09.89,Z79.01  
CPT: 33361-33496,33530,33620,33621,33768,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,  
98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-  
99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,  
G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

- Line: 187**  
Condition: CUSHING'S SYNDROME; HYPERALDOSTERONISM, OTHER CORTICOADRENAL OVERACTIVITY, MEDULLOADRENAL HYPERFUNCTION (See Guideline Notes 64,65,93)  
Treatment: MEDICAL THERAPY/ADRENALECTOMY  
ICD-10: E24.0,E24.2-E24.9,E26.01-E26.9,E27.0,E27.5-E27.8,E30.1-E30.8,E34.2  
CPT: 11981-11983,60540,60545,60650,61546,62100,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9560
- Line: 188**  
Condition: CONGENITAL TRICUSPID ATRESIA AND STENOSIS (See Guideline Notes 64,65)  
Treatment: REPAIR  
ICD-10: Q22.4,Q22.6-Q22.9  
CPT: 33460-33464,33496,33608,33615,33617,33620,33621,33735-33750,33766,33768,33946-33966,33969,33984-33989,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 189**  
Condition: CHRONIC ISCHEMIC HEART DISEASE (See Guideline Notes 49,64,65,89)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: I20.1-I20.9,I23.6,I25.10,I25.111-I25.6,I25.701-I25.709,I25.711-I25.719,I25.721-I25.729,I25.731-I25.739,I25.751-I25.759,I25.761-I25.769,I25.791-I25.9,I51.0,I51.3,Q27.30,Q27.4,Q28.0-Q28.1,Z45.010-Z45.09,Z79.01  
CPT: 33202,33206-33210,33212-33229,33233-33238,33361-33430,33465,33475,33477,33500,33508-33542,33572,33681,33922,33973,33974,35001,35182,35189,35226,35256,35286,35572,35600,92920-92938,92943,92944,92960-92998,93279-93284,93286-93289,93292-93296,93355,93724,93745,93792-93798,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,K0606-K0609,S0340-S0342,S2205-S2209
- Line: 190**  
Condition: NEOPLASMS OF ISLETS OF LANGERHANS (See Guideline Note 65)  
Treatment: EXCISION OF TUMOR  
ICD-10: C25.4,D13.7  
CPT: 43260-43265,43274-43278,47542,48120,48140,49324,49325,49421,49422,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 191**  
Condition: CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER (See Guideline Notes 3,7,11,12,16,26,64,65,79,88,148)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY, RADIATION THERAPY AND BREAST RECONSTRUCTION  
ICD-10: C50.011-C50.929,D05.00-D05.92,D48.60-D48.62,D61.810,G89.3,N65.0-N65.1,Z15.01-Z15.02,Z40.01-Z40.03,Z42.1,Z44.30-Z44.32,Z45.811-Z45.819,Z51.0,Z51.11-Z51.12,Z79.810,Z80.3,Z85.3,Z90.10-Z90.13  
CPT: 11970,13100-13102,19110,19120-19126,19296-19298,19301-19318,19328-19369,32553,38740,38745,49411,58300,58301,58661,58940,77014,77261-77295,77300-77370,77385-77387,77402-77417,77427,77431,77470,77520-77763,77770-77790,79005-79445,81519,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S2066-S2068,S9537,S9560
- Line: 192**  
Condition: HEREDITARY ANGIOEDEMA (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: D81.810,D84.1,T78.3XXA-T78.3XXD  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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- Line: 193**  
Condition: AUTISM SPECTRUM DISORDERS (See Guideline Notes 65,75)  
Treatment: MEDICAL THERAPY/BEHAVIORAL MODIFICATION INCLUDING APPLIED BEHAVIOR ANALYSIS  
ICD-10: F84.0,F84.3-F84.9  
CPT: 0359T-0374T,90785,90832-90840,90846-90849,90882,90887,93792,93793,96118,98966-98969,99051,99060,99201-99215,99224-99226,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0023,H0032,H0034,H0038,H2010,H2014,H2027,H2032,S9484
- Line: 194**  
Condition: HEREDITARY ANEMIAS, HEMOGLOBINOPATHIES, AND DISORDERS OF THE SPLEEN (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: D47.4,D55.0-D55.9,D56.0-D56.9,D57.00-D57.20,D57.211-D57.819,D58.0-D58.9,D64.4,D64.89,D73.0-D73.2,D73.4-D73.5,D73.81-D73.89,D74.0-D74.9,D75.0-D75.1,D75.81,D77,Q89.01-Q89.09  
CPT: 36514,36516,38100-38102,38120,47562,47563,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99195,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9355
- Line: 195**  
Condition: ACUTE PANCREATITIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: B25.2,B26.3,K85.00-K85.92,Z80.41  
CPT: 43260-43265,43273-43278,47542,47562-47564,47600-47620,48000-48020,48105,48120,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 196**  
Condition: SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN (See Guideline Notes 6,64,65,90)  
Treatment: BURR HOLES, CRANIECTOMY/CRANIOTOMY  
ICD-10: G93.5-G93.6,I60.00-I60.9,I61.0-I61.9,I62.00-I62.9,I67.1,I67.5,Q28.2-Q28.3,S06.1X0A-S06.1X0D,S06.1X1A-S06.1X1D,S06.1X2A-S06.1X2D,S06.1X3A-S06.1X3D,S06.1X4A-S06.1X4D,S06.1X5A-S06.1X5D,S06.1X6A-S06.1X6D,S06.1X9A-S06.1X9D,S06.340A-S06.340D,S06.341A-S06.341D,S06.342A-S06.342D,S06.343A-S06.343D,S06.344A-S06.344D,S06.345A-S06.345D,S06.346A-S06.346D,S06.347A-S06.347D,S06.349D,S06.350A-S06.350D,S06.351A-S06.351D,S06.352A-S06.352D,S06.353A-S06.353D,S06.354A-S06.354D,S06.355A-S06.355D,S06.356A-S06.356D,S06.357A-S06.357D,S06.359D,S06.360A-S06.360D,S06.361A-S06.361D,S06.362A-S06.362D,S06.363A-S06.363D,S06.364A-S06.364D,S06.365A-S06.365D,S06.366A-S06.366D,S06.367A-S06.367D,S06.369D,S06.371A-S06.371D,S06.372A-S06.372D,S06.373A-S06.373D,S06.374A-S06.374D,S06.375A-S06.375D,S06.376A-S06.376D,S06.377A-S06.377D,S06.380A-S06.380D,S06.381A-S06.381D,S06.382A-S06.382D,S06.383A-S06.383D,S06.384A-S06.384D,S06.385A-S06.385D,S06.386A-S06.386D,S06.387A-S06.387D,S06.4X0A-S06.4X0D,S06.4X1A-S06.4X1D,S06.4X2A-S06.4X2D,S06.4X3A-S06.4X3D,S06.4X4A-S06.4X4D,S06.4X5A-S06.4X5D,S06.4X6A-S06.4X6D,S06.4X7A-S06.4X7D,S06.5X0A-S06.5X0D,S06.5X1A-S06.5X1D,S06.5X2A-S06.5X2D,S06.5X3A-S06.5X3D,S06.5X4A-S06.5X4D,S06.5X5A-S06.5X5D,S06.5X6A-S06.5X6D,S06.5X7A-S06.5X7D,S06.5X9A-S06.5X9D,S06.6X0A-S06.6X0D,S06.6X1A-S06.6X1D,S06.6X2A-S06.6X2D,S06.6X3A-S06.6X3D,S06.6X4A-S06.6X4D,S06.6X5A-S06.6X5D,S06.6X6A-S06.6X6D,S06.6X9A-S06.6X9D  
CPT: 31290,31291,61107-61120,61150-61154,61210,61312-61316,61322,61323,61343,61522-61626,61680-61711,61781-61783,62100,62143,62160,62220,62223,62272,77263-77290,77295,77300,77306,77307,77332-77336,77370-77372,77385-77387,77402-77412,77432,92507,92508,92521-92526,92607-92609,92633,93792,93793,96150-96155,97012,97110-97127,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513-G0515,G6001-G6017,S9152
- Line: 197**  
Condition: BURN, PARTIAL THICKNESS WITHOUT VITAL SITE REQUIRING GRAFTING, UP TO 30% OF BODY SURFACE (See Guideline Notes 6,64,65)  
Treatment: FREE SKIN GRAFT, MEDICAL THERAPY  
ICD-10: L00,T20.25XA-T20.25XD,T20.26XA-T20.26XD,T20.35XA-T20.35XD,T20.36XA-T20.36XD,T20.65XA-T20.65XD,T20.66XA-T20.66XD,T20.75XA-T20.75XD,T20.76XA-T20.76XD,T21.20XA-T21.20XD,T21.21XA-T21.21XD,T21.22XA-T21.22XD,T21.23XA-T21.23XD,T21.24XA-T21.24XD,T21.25XA-T21.25XD,T21.29XA-T21.29XD,T21.30XA-T21.30XD,T21.31XA-T21.31XD,T21.32XA-T21.32XD,T21.33XA-T21.33XD,T21.34XA-T21.34XD,T21.35XA-T21.35XD,T21.39XA-T21.39XD,T21.60XA-T21.60XD,T21.61XA-T21.61XD,T21.62XA-T21.62XD,T21.63XA-T21.63XD,T21.64XA-T21.64XD,T21.65XA-T21.65XD,T21.69XA-T21.69XD,T21.70XA-T21.70XD,T21.71XA-T21.71XD,T21.72XA-T21.72XD,T21.73XA-T21.73XD,T21.74XA-T21.74XD,T21.75XA-T21.75XD,



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T21.79XA-T21.79XD,T22.20XA-T22.20XD,T22.211A-T22.211D,T22.212A-T22.212D,T22.219A-T22.219D,  
T22.221A-T22.221D,T22.222A-T22.222D,T22.229A-T22.229D,T22.231A-T22.231D,T22.232A-T22.232D,  
T22.239A-T22.239D,T22.241A-T22.241D,T22.242A-T22.242D,T22.249A-T22.249D,T22.251A-T22.251D,  
T22.252A-T22.252D,T22.259A-T22.259D,T22.261A-T22.261D,T22.262A-T22.262D,T22.269A-T22.269D,  
T22.291A-T22.291D,T22.292A-T22.292D,T22.299A-T22.299D,T22.30XA-T22.30XD,T22.311A-T22.311D,  
T22.312A-T22.312D,T22.319A-T22.319D,T22.321A-T22.321D,T22.322A-T22.322D,T22.329A-T22.329D,  
T22.331A-T22.331D,T22.332A-T22.332D,T22.339A-T22.339D,T22.341A-T22.341D,T22.342A-T22.342D,  
T22.349A-T22.349D,T22.351A-T22.351D,T22.352A-T22.352D,T22.359A-T22.359D,T22.361A-T22.361D,  
T22.362A-T22.362D,T22.369A-T22.369D,T22.391A-T22.391D,T22.392A-T22.392D,T22.399A-T22.399D,  
T22.60XA-T22.60XD,T22.611A-T22.611D,T22.612A-T22.612D,T22.619A-T22.619D,T22.621A-T22.621D,  
T22.622A-T22.622D,T22.629A-T22.629D,T22.631A-T22.631D,T22.632A-T22.632D,T22.639A-T22.639D,  
T22.641A-T22.641D,T22.642A-T22.642D,T22.649A-T22.649D,T22.651A-T22.651D,T22.652A-T22.652D,  
T22.659A-T22.659D,T22.661A-T22.661D,T22.662A-T22.662D,T22.669A-T22.669D,T22.691A-T22.691D,  
T22.692A-T22.692D,T22.699A-T22.699D,T22.70XA-T22.70XD,T22.711A-T22.711D,T22.712A-T22.712D,  
T22.719A-T22.719D,T22.721A-T22.721D,T22.722A-T22.722D,T22.729A-T22.729D,T22.731A-T22.731D,  
T22.732A-T22.732D,T22.739A-T22.739D,T22.741A-T22.741D,T22.742A-T22.742D,T22.749A-T22.749D,  
T22.751A-T22.751D,T22.752A-T22.752D,T22.759A-T22.759D,T22.761A-T22.761D,T22.762A-T22.762D,  
T22.769A-T22.769D,T22.791A-T22.791D,T22.792A-T22.792D,T22.799A-T22.799D,T23.201A-T23.201D,  
T23.202A-T23.202D,T23.209A-T23.209D,T23.211A-T23.211D,T23.212A-T23.212D,T23.219A-T23.219D,  
T23.221A-T23.221D,T23.222A-T23.222D,T23.229A-T23.229D,T23.231A-T23.231D,T23.232A-T23.232D,  
T23.239A-T23.239D,T23.241A-T23.241D,T23.242A-T23.242D,T23.249A-T23.249D,T23.261A-T23.261D,  
T23.262A-T23.262D,T23.269A-T23.269D,T23.271A-T23.271D,T23.272A-T23.272D,T23.279A-T23.279D,  
T23.291A-T23.291D,T23.292A-T23.292D,T23.299A-T23.299D,T23.301A-T23.301D,T23.302A-T23.302D,  
T23.309A-T23.309D,T23.311A-T23.311D,T23.312A-T23.312D,T23.319A-T23.319D,T23.321A-T23.321D,  
T23.322A-T23.322D,T23.329A-T23.329D,T23.331A-T23.331D,T23.332A-T23.332D,T23.339A-T23.339D,  
T23.341A-T23.341D,T23.342A-T23.342D,T23.349A-T23.349D,T23.361A-T23.361D,T23.362A-T23.362D,  
T23.369A-T23.369D,T23.371A-T23.371D,T23.372A-T23.372D,T23.379A-T23.379D,T23.391A-T23.391D,  
T23.392A-T23.392D,T23.399A-T23.399D,T23.601A-T23.601D,T23.602A-T23.602D,T23.609A-T23.609D,  
T23.611A-T23.611D,T23.612A-T23.612D,T23.619A-T23.619D,T23.621A-T23.621D,T23.622A-T23.622D,  
T23.629A-T23.629D,T23.631A-T23.631D,T23.632A-T23.632D,T23.639A-T23.639D,T23.641A-T23.641D,  
T23.642A-T23.642D,T23.649A-T23.649D,T23.661A-T23.661D,T23.662A-T23.662D,T23.669A-T23.669D,  
T23.671A-T23.671D,T23.672A-T23.672D,T23.679A-T23.679D,T23.691A-T23.691D,T23.692A-T23.692D,  
T23.699A-T23.699D,T23.701A-T23.701D,T23.702A-T23.702D,T23.709A-T23.709D,T23.711A-T23.711D,  
T23.712A-T23.712D,T23.719A-T23.719D,T23.721A-T23.721D,T23.722A-T23.722D,T23.729A-T23.729D,  
T23.731A-T23.731D,T23.732A-T23.732D,T23.739A-T23.739D,T23.741A-T23.741D,T23.742A-T23.742D,  
T23.749A-T23.749D,T23.761A-T23.761D,T23.762A-T23.762D,T23.769A-T23.769D,T23.771A-T23.771D,  
T23.772A-T23.772D,T23.779A-T23.779D,T23.791A-T23.791D,T23.792A-T23.792D,T23.799A-T23.799D,  
T24.201A-T24.201D,T24.202A-T24.202D,T24.209A-T24.209D,T24.211A-T24.211D,T24.212A-T24.212D,  
T24.219A-T24.219D,T24.221A-T24.221D,T24.222A-T24.222D,T24.229A-T24.229D,T24.231A-T24.231D,  
T24.232A-T24.232D,T24.239A-T24.239D,T24.291A-T24.291D,T24.292A-T24.292D,T24.299A-T24.299D,  
T24.301A-T24.301D,T24.302A-T24.302D,T24.309A-T24.309D,T24.311A-T24.311D,T24.312A-T24.312D,  
T24.319A-T24.319D,T24.321A-T24.321D,T24.322A-T24.322D,T24.329A-T24.329D,T24.331A-T24.331D,  
T24.332A-T24.332D,T24.339A-T24.339D,T24.391A-T24.391D,T24.392A-T24.392D,T24.399A-T24.399D,  
T24.601A-T24.601D,T24.602A-T24.602D,T24.609A-T24.609D,T24.611A-T24.611D,T24.612A-T24.612D,  
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T24.632A-T24.632D,T24.639A-T24.639D,T24.691A-T24.691D,T24.692A-T24.692D,T24.699A-T24.699D,  
T24.701A-T24.701D,T24.702A-T24.702D,T24.709A-T24.709D,T24.711A-T24.711D,T24.712A-T24.712D,  
T24.719A-T24.719D,T24.721A-T24.721D,T24.722A-T24.722D,T24.729A-T24.729D,T24.731A-T24.731D,  
T24.732A-T24.732D,T24.739A-T24.739D,T24.791A-T24.791D,T24.792A-T24.792D,T24.799A-T24.799D,  
T25.211A-T25.211D,T25.212A-T25.212D,T25.219A-T25.219D,T25.231A-T25.231D,T25.232A-T25.232D,  
T25.239A-T25.239D,T25.291A-T25.291D,T25.292A-T25.292D,T25.299A-T25.299D,T25.311A-T25.311D,  
T25.312A-T25.312D,T25.319A-T25.319D,T25.331A-T25.331D,T25.332A-T25.332D,T25.339A-T25.339D,  
T25.391A-T25.391D,T25.392A-T25.392D,T25.399A-T25.399D,T25.611A-T25.611D,T25.612A-T25.612D,  
T25.619A-T25.619D,T25.631A-T25.631D,T25.632A-T25.632D,T25.639A-T25.639D,T25.691A-T25.691D,  
T25.692A-T25.692D,T25.699A-T25.699D,T25.711A-T25.711D,T25.712A-T25.712D,T25.719A-T25.719D,  
T25.731A-T25.731D,T25.732A-T25.732D,T25.739A-T25.739D,T25.791A-T25.791D,T25.792A-T25.792D,  
T25.799A-T25.799D

CPT: 11000,11042,11045,11960-11971,15002-15005,15271-15278,16000-16036,92507,92508,92521-92524,92607-  
92609,92633,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,  
98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-  
99480,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,  
G0513,G0514,S9152

**Line: 198**

Condition: CONGENITAL LUNG ANOMALIES (See Guideline Notes 64,65)

Treatment: MEDICAL AND SURGICAL TREATMENT

ICD-10: Q33.0,Q33.2-Q33.4,Q33.6

CPT: 31601,31820,31825,32140,32141,32480-32488,32501,32505-32507,32662,32663,32666-32670,32800,93792,  
93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,  
99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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<b>Line:</b>	<b>199</b>
Condition:	CHRONIC HEPATITIS; VIRAL HEPATITIS (See Guideline Notes 64,65,76)
Treatment:	MEDICAL THERAPY
ICD-10:	B15.0-B15.9,B16.0-B16.9,B17.0,B17.10-B17.9,B18.0-B18.9,B19.0,B19.10-B19.9,B25.1,K73.0-K73.9,K74.1-K74.2,K75.4,K75.81,K76.0,K76.4
CPT:	91200,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>200</b>
Condition:	CANCER OF SOFT TISSUE (See Guideline Notes 7,11,12,19,64,65)
Treatment:	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10:	C38.0,C45.2,C47.0,C47.10-C47.9,C49.0,C49.10-C49.9,D48.1-D48.2,D61.810,G89.3,Z51.0,Z51.11-Z51.12
CPT:	20555,21011-21016,21121,21552-21558,21930-21936,22900-22905,23071-23078,24071-24079,25071-25078,26111-26118,27043-27049,27059,27075-27078,27130,27327-27329,27337,27339,27364,27615-27619,27632,27634,28039-28047,32553,33120,33130,49203-49205,49411,64774-64783,69110,69120,69145-69155,77014,77261-77295,77300-77370,77385-77387,77402-77432,77469,77470,77761-77763,77770-77790,78811-78816,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537
<b>Line:</b>	<b>201</b>
Condition:	CANCER OF BONES (See Guideline Notes 6,7,11,12,16,19,64,65,100)
Treatment:	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10:	C40.00-C40.92,C41.0-C41.9,C79.51-C79.52,D48.0,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.830
CPT:	19260-19272,20930-20938,20955-20973,21025,21026,21034,21044,21045,21081,21610,21620,22532-22819,22853,22854,22859,23140,23200-23330,23470-23474,23900,24150-24155,24363,24370,24371,24498,24900-24931,25110-25119,25210-25240,25320,25335,25337,25391-25393,25441-25447,25450-25492,25505,25810-25931,26910-26952,27025,27054,27065-27067,27075-27078,27130,27187,27290,27334,27335,27365,27465-27468,27495,27590-27598,27635-27647,27656,27745,27880-27889,28800-28825,31200,31201,31225,31600,32553,32900,36680,38720,38724,49411,61500,61583,61601,63081-63103,63276,63295,63620,63621,67412,69970,77014,77261-77295,77300-77307,77321-77370,77385-77387,77401-77431,77469,77470,77520-77525,78811-78816,79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	D5934,D5935,D5984,D5992,D5993,D7440,D7441,G0157-G0161,G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537
<b>Line:</b>	<b>202</b>
Condition:	CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS (See Guideline Notes 6,64,65,86,90,92,121)
Treatment:	CONSULTATION/MEDICATION MANAGEMENT/BEHAVIORAL SUPPORT
ICD-10:	E51.2,F01.50-F01.51,F02.80-F02.81,F03.90-F03.91,F04,F06.0-F06.2,F06.30-F06.8,F07.0,F07.81,F10.26-F10.27,F10.96-F10.97,F13.26-F13.27,F13.96-F13.97,F18.17,F18.27,F18.97,F19.16-F19.17,F19.26-F19.27,F19.96-F19.97,G30.0-G30.9,G31.01-G31.2,G31.83
CPT:	90785,90832-90840,90846-90853,90882,90887,93792,93793,96118,97127,97161-97168,98966-98969,99051,99060,99201-99239,99304-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS:	G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513-G0515,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9484,T1005
<b>Line:</b>	<b>203</b>
Condition:	SLEEP APNEA, NARCOLEPSY AND REM BEHAVIORAL DISORDER (See Guideline Notes 27,64,65,118)
Treatment:	MEDICAL AND SURGICAL TREATMENT
ICD-10:	G47.30-G47.31,G47.33-G47.39,G47.411-G47.429,G47.52
CPT:	21193-21235,30117,30140,30520,31600,31601,31610,31820,31825,42140-42160,42820-42836,93792,93793,94660,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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- Line: 204**  
Condition: DEPRESSION AND OTHER MOOD DISORDERS, MILD OR MODERATE (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F32.0-F32.1,F32.81-F32.89,F33.8,F34.0,F34.81-F34.89,F39,N94.3  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,97810-97814,98966-98969,99051,99060,99201-99239,99324-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005
- Line: 205**  
Condition: PNEUMOCOCCAL PNEUMONIA, OTHER BACTERIAL PNEUMONIA, BRONCHOPNEUMONIA (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A01.03,A02.22,A20.2,A21.2,A48.1,A54.84,A70,J13-J14,J15.0-J15.1,J15.20,J15.211-J15.9,J16.0-J16.8,J17,J18.0-J18.1,J18.8-J18.9,J69.0-J69.8  
CPT: 31600,31645,31646,93792,93793,94002-94005,94640,94660-94668,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 206**  
Condition: SUPERFICIAL ABSCESES AND CELLULITIS (See Coding Specification Below) (See Guideline Notes 62,64,65,113)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: A46,A48.2,A48.4,B78.1,E83.2,H00.031-H00.039,H60.00-H60.23,I89.1,J34.0,J38.3,J38.7,K12.2,K14.0,K61.0-K61.4,L01.00-L01.1,L02.01-L02.13,L02.211-L02.93,L03.011-L03.91,L05.01-L05.02,L08.0,L08.81-L08.9,L60.0,L98.3,N34.0,N41.2,N41.4-N41.8,N43.1,N48.21-N48.29,N49.1-N49.2,N49.8-N49.9,N61.0-N61.1,N75.1,N76.4  
CPT: 10030,10060-10081,10160,11000-11047,11730-11750,11765-11772,19020,20005,20102,21501,21502,22010,22015,23030,23930,25028,26010,26011,26990,27301,27603,28001-28003,29130,30020,31300-31420,31511-31513,31530,31531,31540-31546,31560-31573,31577,31578,31587,31595,31600,31601,31820,31825,40801,41000-41009,41015-41018,41800,42000,45005,45020,46020,46040-46060,46270,53040,53060,53270,54700,55100,55720,55725,56405,56420,56740,60280,67700,69000,92002-92014,93792,93793,96150-96155,96920-96922,97605-97608,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- ICD-10 J38.3 is included on Line 206 for treatment of abscesses and cellulitis of the vocal cords; it is included on Line 557 for treatment of spastic dysphonia.
- Line: 207**  
Condition: ZOONOTIC BACTERIAL DISEASES (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A20.0-A20.1,A20.8-A20.9,A21.0-A21.1,A21.3-A21.9,A22.0-A22.2,A22.8-A22.9,A23.0-A23.9,A24.0-A24.9,A25.0-A25.9,A26.0,A26.8-A26.9,A27.0,A27.89-A27.9,A28.0-A28.9,A32.0,A32.81,A32.89-A32.9,Z03.810-Z03.818  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 208**  
Condition: DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT (See Guideline Notes 6,62,64,65,133)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: S01.00XA-S01.00XD,S01.01XA-S01.01XD,S01.02XA-S01.02XD,S01.03XA-S01.03XD,S01.04XA-S01.04XD,S01.05XA-S01.05XD,S01.111A-S01.111D,S01.112A-S01.112D,S01.119A-S01.119D,S01.121A-S01.121D,S01.122A-S01.122D,S01.129A-S01.129D,S01.131A-S01.131D,S01.132A-S01.132D,S01.139A-S01.139D,S01.141A-S01.141D,S01.142A-S01.142D,S01.149A-S01.149D,S01.151A-S01.151D,S01.152A-S01.152D,S01.159A-S01.159D,S01.20XA-S01.20XD,S01.21XA-S01.21XD,S01.22XA-S01.22XD,S01.23XA-S01.23XD,S01.24XA-S01.24XD,S01.25XA-S01.25XD,S01.301A-S01.301D,S01.302A-S01.302D,S01.309A-S01.309D,S01.311A-S01.311D,S01.312A-S01.312D,S01.319A-S01.319D,S01.321A-S01.321D,S01.322A-S01.322D,S01.329A-S01.329D,S01.331A-S01.331D,S01.332A-S01.332D,S01.339A-S01.339D,S01.341A-S01.341D,S01.342A-S01.342D,S01.349A-S01.349D,S01.351A-S01.351D,S01.352A-S01.352D,S01.359A-S01.359D,S01.401A-S01.401D,S01.402A-S01.402D,S01.409A-S01.409D,S01.411A-S01.411D,S01.412A-S01.412D,S01.419A-S01.419D,S01.421A-S01.421D,S01.422A-S01.422D,S01.429A-S01.429D,S01.431A-S01.431D,S01.432A-S01.432D,S01.439A-S01.439D,S01.441A-S01.441D,S01.442A-S01.442D,S01.449A-S01.449D,S01.451A-S01.451D,S01.452A-S01.452D,S01.459A-S01.459D,S01.511A-S01.511D,S01.521A-S01.521D,S01.522A-S01.522D,S01.531A-S01.531D,S01.541A-S01.541D,S01.542A-S01.542D,S01.551A-S01.551D,S01.80XA-S01.80XD,S01.81XA-S01.81XD,S01.82XA-S01.82XD,S01.83XA-S01.83XD,S01.84XA-S01.84XD,S01.85XA-S01.85XD,S01.90XA-S01.90XD,S01.91XA-S01.91XD,S01.92XA-S01.92XD,S01.93XA-S01.93XD,



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S01.94XA-S01.94XD,S01.95XA-S01.95XD,S08.0XXA-S08.0XXD,S08.111A-S08.111D,S08.112A-S08.112D,  
S08.119A-S08.119D,S08.121A-S08.121D,S08.122A-S08.122D,S08.129A-S08.129D,S08.811A-S08.811D,  
S08.812A-S08.812D,S08.89XA-S08.89XD,S09.12XA-S09.12XD,S09.301A-S09.301D,S09.302A-S09.302D,  
S09.309A-S09.309D,S09.311A-S09.311D,S09.312A-S09.312D,S09.313A-S09.313D,S09.319A-S09.319D,  
S09.391A-S09.391D,S09.392A-S09.392D,S09.399A-S09.399D,S09.91XA-S09.91XD,S14.3XXA-S14.3XXD,  
S14.4XXA-S14.4XXD,S14.5XXA-S14.5XXD,S14.8XXA-S14.8XXD,S14.9XXA-S14.9XXD,S21.001A-S21.001D,  
S21.002A-S21.002D,S21.009A-S21.009D,S21.011A-S21.011D,S21.012A-S21.012D,S21.019A-S21.019D,  
S21.021A-S21.021D,S21.022A-S21.022D,S21.029A-S21.029D,S21.031A-S21.031D,S21.032A-S21.032D,  
S21.039A-S21.039D,S21.041A-S21.041D,S21.042A-S21.042D,S21.049A-S21.049D,S21.051A-S21.051D,  
S21.052A-S21.052D,S21.059A-S21.059D,S21.101A-S21.101D,S21.102A-S21.102D,S21.109A-S21.109D,  
S21.111A-S21.111D,S21.112A-S21.112D,S21.119A-S21.119D,S21.121A-S21.121D,S21.122A-S21.122D,  
S21.129A-S21.129D,S21.131A-S21.131D,S21.132A-S21.132D,S21.139A-S21.139D,S21.141A-S21.141D,  
S21.142A-S21.142D,S21.149A-S21.149D,S21.151A-S21.151D,S21.152A-S21.152D,S21.159A-S21.159D,  
S21.201A-S21.201D,S21.202A-S21.202D,S21.209A-S21.209D,S21.211A-S21.211D,S21.212A-S21.212D,  
S21.219A-S21.219D,S21.221A-S21.221D,S21.222A-S21.222D,S21.229A-S21.229D,S21.231A-S21.231D,  
S21.232A-S21.232D,S21.239A-S21.239D,S21.241A-S21.241D,S21.242A-S21.242D,S21.249A-S21.249D,  
S21.251A-S21.251D,S21.252A-S21.252D,S21.259A-S21.259D,S21.90XA-S21.90XD,S21.91XA-S21.91XD,  
S21.92XA-S21.92XD,S21.93XA-S21.93XD,S21.94XA-S21.94XD,S21.95XA-S21.95XD,S24.3XXA-S24.3XXD,  
S24.4XXA-S24.4XXD,S24.8XXA-S24.8XXD,S24.9XXA-S24.9XXD,S28.1XXA-S28.1XXD,S28.211A-S28.211D,  
S28.212A-S28.212D,S28.219A-S28.219D,S28.221A-S28.221D,S28.222A-S28.222D,S28.229A-S28.229D,  
S29.021A-S29.021D,S29.022A-S29.022D,S29.029A-S29.029D,S31.000A-S31.000D,S31.010A-S31.010D,  
S31.020A-S31.020D,S31.030A-S31.030D,S31.040A-S31.040D,S31.050A-S31.050D,S31.100A-S31.100D,  
S31.101A-S31.101D,S31.102A-S31.102D,S31.103A-S31.103D,S31.104A-S31.104D,S31.105A-S31.105D,  
S31.109A-S31.109D,S31.110A-S31.110D,S31.111A-S31.111D,S31.112A-S31.112D,S31.113A-S31.113D,  
S31.114A-S31.114D,S31.115A-S31.115D,S31.119A-S31.119D,S31.120A-S31.120D,S31.121A-S31.121D,  
S31.122A-S31.122D,S31.123A-S31.123D,S31.124A-S31.124D,S31.125A-S31.125D,S31.129A-S31.129D,  
S31.130A-S31.130D,S31.131A-S31.131D,S31.132A-S31.132D,S31.133A-S31.133D,S31.134A-S31.134D,  
S31.135A-S31.135D,S31.139A-S31.139D,S31.140A-S31.140D,S31.141A-S31.141D,S31.142A-S31.142D,  
S31.143A-S31.143D,S31.144A-S31.144D,S31.145A-S31.145D,S31.149A-S31.149D,S31.150A-S31.150D,  
S31.151A-S31.151D,S31.152A-S31.152D,S31.153A-S31.153D,S31.154A-S31.154D,S31.155A-S31.155D,  
S31.159A-S31.159D,S31.20XA-S31.20XD,S31.21XA-S31.21XD,S31.22XA-S31.22XD,S31.23XA-S31.23XD,  
S31.24XA-S31.24XD,S31.25XA-S31.25XD,S31.30XA-S31.30XD,S31.31XA-S31.31XD,S31.32XA-S31.32XD,  
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PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

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S76.029A-S76.029D,S76.121A-S76.121D,S76.122A-S76.122D,S76.129A-S76.129D,S76.221A-S76.221D,



PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

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S81.839A-S81.839D,S81.841A-S81.841D,S81.842A-S81.842D,S81.849A-S81.849D,S81.851A-S81.851D,  
S81.852A-S81.852D,S81.859A-S81.859D,S84.00XA-S84.00XD,S84.01XA-S84.01XD,S84.02XA-S84.02XD,  
S84.10XA-S84.10XD,S84.11XA-S84.11XD,S84.12XA-S84.12XD,S84.20XA-S84.20XD,S84.21XA-S84.21XD,  
S84.22XA-S84.22XD,S84.801A-S84.801D,S84.802A-S84.802D,S84.809A-S84.809D,S84.90XA-S84.90XD,  
S84.91XA-S84.91XD,S84.92XA-S84.92XD,S86.021A-S86.021D,S86.022A-S86.022D,S86.029A-S86.029D,  
S86.121A-S86.121D,S86.122A-S86.122D,S86.129A-S86.129D,S86.221A-S86.221D,S86.222A-S86.222D,  
S86.229A-S86.229D,S86.321A-S86.321D,S86.322A-S86.322D,S86.329A-S86.329D,S86.821A-S86.821D,  
S86.822A-S86.822D,S86.829A-S86.829D,S86.921A-S86.921D,S86.922A-S86.922D,S86.929A-S86.929D,  
S91.001A-S91.001D,S91.002A-S91.002D,S91.009A-S91.009D,S91.011A-S91.011D,S91.012A-S91.012D,  
S91.019A-S91.019D,S91.021A-S91.021D,S91.022A-S91.022D,S91.029A-S91.029D,S91.031A-S91.031D,  
S91.032A-S91.032D,S91.039A-S91.039D,S91.041A-S91.041D,S91.042A-S91.042D,S91.049A-S91.049D,  
S91.051A-S91.051D,S91.052A-S91.052D,S91.059A-S91.059D,S91.101A-S91.101D,S91.102A-S91.102D,  
S91.103A-S91.103D,S91.104A-S91.104D,S91.105A-S91.105D,S91.106A-S91.106D,S91.109A-S91.109D,  
S91.111A-S91.111D,S91.112A-S91.112D,S91.113A-S91.113D,S91.114A-S91.114D,S91.115A-S91.115D,  
S91.116A-S91.116D,S91.119A-S91.119D,S91.121A-S91.121D,S91.122A-S91.122D,S91.123A-S91.123D,  
S91.124A-S91.124D,S91.125A-S91.125D,S91.126A-S91.126D,S91.129A-S91.129D,S91.131A-S91.131D,  
S91.132A-S91.132D,S91.133A-S91.133D,S91.134A-S91.134D,S91.135A-S91.135D,S91.136A-S91.136D,  
S91.139A-S91.139D,S91.141A-S91.141D,S91.142A-S91.142D,S91.143A-S91.143D,S91.144A-S91.144D,  
S91.145A-S91.145D,S91.146A-S91.146D,S91.149A-S91.149D,S91.151A-S91.151D,S91.152A-S91.152D,  
S91.153A-S91.153D,S91.154A-S91.154D,S91.155A-S91.155D,S91.156A-S91.156D,S91.159A-S91.159D,  
S91.201A-S91.201D,S91.202A-S91.202D,S91.203A-S91.203D,S91.204A-S91.204D,S91.205A-S91.205D,  
S91.206A-S91.206D,S91.209A-S91.209D,S91.211A-S91.211D,S91.212A-S91.212D,S91.213A-S91.213D,  
S91.214A-S91.214D,S91.215A-S91.215D,S91.216A-S91.216D,S91.219A-S91.219D,S91.221A-S91.221D,  
S91.222A-S91.222D,S91.223A-S91.223D,S91.224A-S91.224D,S91.225A-S91.225D,S91.226A-S91.226D,  
S91.229A-S91.229D,S91.231A-S91.231D,S91.232A-S91.232D,S91.233A-S91.233D,S91.234A-S91.234D,  
S91.235A-S91.235D,S91.236A-S91.236D,S91.239A-S91.239D,S91.241A-S91.241D,S91.242A-S91.242D,  
S91.243A-S91.243D,S91.244A-S91.244D,S91.245A-S91.245D,S91.246A-S91.246D,S91.249A-S91.249D,  
S91.251A-S91.251D,S91.252A-S91.252D,S91.253A-S91.253D,S91.254A-S91.254D,S91.255A-S91.255D,  
S91.256A-S91.256D,S91.259A-S91.259D,S91.301A-S91.301D,S91.302A-S91.302D,S91.309A-S91.309D,  
S91.311A-S91.311D,S91.312A-S91.312D,S91.319A-S91.319D,S91.321A-S91.321D,S91.322A-S91.322D,  
S91.329A-S91.329D,S91.331A-S91.331D,S91.332A-S91.332D,S91.339A-S91.339D,S91.341A-S91.341D,  
S91.342A-S91.342D,S91.349A-S91.349D,S91.351A-S91.351D,S91.352A-S91.352D,S91.359A-S91.359D,  
S94.00XA-S94.00XD,S94.01XA-S94.01XD,S94.02XA-S94.02XD,S94.10XA-S94.10XD,S94.11XA-S94.11XD,  
S94.12XA-S94.12XD,S94.20XA-S94.20XD,S94.21XA-S94.21XD,S94.22XA-S94.22XD,S94.30XA-S94.30XD,  
S94.31XA-S94.31XD,S94.32XA-S94.32XD,S94.8X1A-S94.8X1D,S94.8X2A-S94.8X2D,S94.8X9A-S94.8X9D,  
S94.90XA-S94.90XD,S94.91XA-S94.91XD,S94.92XA-S94.92XD,S95.001A-S95.001D,S95.002A-S95.002D,  
S95.009A-S95.009D,S95.011A-S95.011D,S95.012A-S95.012D,S95.019A-S95.019D,S95.091A-S95.091D,  
S95.092A-S95.092D,S95.099A-S95.099D,S95.101A-S95.101D,S95.102A-S95.102D,S95.109A-S95.109D,  
S95.111A-S95.111D,S95.112A-S95.112D,S95.119A-S95.119D,S95.191A-S95.191D,S95.192A-S95.192D,  
S95.199A-S95.199D,S95.201A-S95.201D,S95.202A-S95.202D,S95.209A-S95.209D,S95.211A-S95.211D,  
S95.212A-S95.212D,S95.219A-S95.219D,S95.291A-S95.291D,S95.292A-S95.292D,S95.299A-S95.299D,  
S95.801A-S95.801D,S95.802A-S95.802D,S95.809A-S95.809D,S95.811A-S95.811D,S95.812A-S95.812D,  
S95.819A-S95.819D,S95.891A-S95.891D,S95.892A-S95.892D,S95.899A-S95.899D,S95.901A-S95.901D,  
S95.902A-S95.902D,S95.909A-S95.909D,S95.911A-S95.911D,S95.912A-S95.912D,S95.919A-S95.919D,  
S95.991A-S95.991D,S95.992A-S95.992D,S95.999A-S95.999D,S96.021A-S96.021D,S96.022A-S96.022D,  
S96.029A-S96.029D,S96.121A-S96.121D,S96.122A-S96.122D,S96.129A-S96.129D,S96.221A-S96.221D,  
S96.222A-S96.222D,S96.229A-S96.229D,S96.821A-S96.821D,S96.822A-S96.822D,S96.829A-S96.829D,  
S96.921A-S96.921D,S96.922A-S96.922D,S96.929A-S96.929D,S98.111A-S98.111D,S98.112A-S98.112D,  
S98.119A-S98.119D,S98.121A-S98.121D,S98.122A-S98.122D,S98.129A-S98.129D,S98.131A-S98.131D,  
S98.132A-S98.132D,S98.139A-S98.139D,S98.141A-S98.141D,S98.142A-S98.142D,S98.149A-S98.149D,  
S98.211A-S98.211D,S98.212A-S98.212D,S98.219A-S98.219D,S98.221A-S98.221D,S98.222A-S98.222D,  
S98.229A-S98.229D,T79.2XXA-T79.2XXD  
CPT: 10120,10121,11000-11047,11730,11732,11750,11760,12001-13160,15002-15005,15845,20101-20150,20525,  
23040,23044,23397,24000,24006,24101,24102,24341,25101-25109,25260-25272,25295-25310,25320,25335,  
25337,25390-25393,25441-25447,25450-25492,25810-25830,25922,26080,26350-26420,26428-26510,26540,  
26591,26951,26990,27310,27372,27603,27830,27831,28022,28024,28140,28200,28210-28825,29075,  
29130,29515,29580,30901-30906,32653,40650-40654,40830,40831,41250-41252,42180,42182,49904,54437-  
54440,54520,54660,54670,56800,57200,57210,57287,64702-64714,64718-64721,64727-64792,64820,64831-  
64862,64872-64911,67930,67935,67950,90675,90676,92002-92014,93792,93793,97110,97112,97140-97168,  
97530,97535,97605-97608,97760,97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-  
99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: D7912,D7920,G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,  
G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

<b>Line:</b>	<b>209</b>
Condition:	CANCER OF UTERUS (See Guideline Notes 7,11,12,64,65)
Treatment:	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10:	C54.0-C54.9,C55,D07.0,D61.810,G89.3,N85.00,N85.02,Z51.0,Z51.11-Z51.12,Z85.42
CPT:	32553,38562,38564,38571-38573,38770,38780,49203-49205,49327,49411,49412,55920,57155,57156,58120,58150-58294,58346,58541-58544,58548-58554,58570-58575,58953-58956,77014,77261-77295,77300-77370,77385-77387,77402-77417,77424-77427,77469,77470,77761-77763,77770-77790,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017
<b>Line:</b>	<b>210</b>
Condition:	RUPTURE OF LIVER (See Guideline Notes 64,65)
Treatment:	SUTURE/REPAIR
ICD-10:	K76.3,K76.5,K77,S36.116A-S36.116D
CPT:	47350-47362,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>211</b>
Condition:	CANCER OF THYROID (See Guideline Notes 7,11,12,19,64,65)
Treatment:	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-10:	C73,D44.0,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.850
CPT:	32553,32674,38700-38724,38746,49411,60200-60271,60512,77014,77261-77295,77300-77307,77321-77370,77385-77387,77401-77427,77469,78811-78816,79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	D5984,G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537
<b>Line:</b>	<b>212</b>
Condition:	NON-SUBSTANCE-RELATED ADDICTIVE BEHAVIORAL DISORDERS (See Guideline Notes 64,65) (Note: This line is not priced as part of the list as funding comes from non-OHP sources)
Treatment:	MEDICAL/PSYCHOTHERAPY
ICD-10:	F63.0
CPT:	90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS:	G0176,G0177,G0248-G0250,G0406-G0408,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0017,H0019,H0023,H0032-H0034,H0036-H0039,H0045,H2010,H2013,H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9484,T1005
<b>Line:</b>	<b>213</b>
Condition:	BULLOUS DERMATOSES OF THE SKIN (See Guideline Notes 64,65)
Treatment:	MEDICAL THERAPY
ICD-10:	L10.0-L10.5,L10.81-L10.9,L12.0-L12.2,L12.8-L12.9,L13.0-L13.9,L14
CPT:	36514,36516,65778-65782,68371,77014,93792,93793,96900,96902,96910-96913,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>214</b>
Condition:	ACUTE PULMONARY HEART DISEASE AND PULMONARY EMBOLI (See Guideline Notes 64,65,147)
Treatment:	MEDICAL AND SURGICAL TREATMENT
ICD-10:	I26.01-I26.99,I27.82,T79.1XXA-T79.1XXD
CPT:	33910-33916,37191-37193,92960-92971,92978-92998,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

- Line: 215**  
Condition: CANCER OF KIDNEY AND OTHER URINARY ORGANS (See Guideline Notes 7,11,12,64,65,96)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C64.1-C64.9,C65.1-C65.9,C68.0-C68.8,C7A.093,C79.00-C79.02,D09.19,D30.00-D30.9,D41.00-D41.3,D41.8,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.50,Z85.528-Z85.59  
CPT: 32553,32674,38746,49203-49205,49411,50125,50220-50290,50340,50391,50542,50543,50545,50546,50548,50553,50557,50572,50650,50660,50825-50840,51530,51550-51597,51700,51720,52214-52250,52281,52282,52354,52355,52450,52500,53210-53220,58200,58960,77014,77261-77290,77295,77300,77306,77307,77321-77370,77385-77387,77402-77417,77424-77432,77469,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537
- Line: 216**  
Condition: CANCER OF STOMACH (See Guideline Notes 7,11,12,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C16.0-C16.9,C49.A0,C49.A2,C49.A9,C7A.092,D00.2,D37.1,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.028  
CPT: 32553,38747,43122,43245,43248,43249,43266,43611-43635,44110-44130,44186,44310,49327,49411,49412,77014,77261-77295,77300-77307,77321-77370,77385-77387,77402-77417,77424-77432,77469,77470,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537
- Line: 217**  
Condition: PORTAL VEIN THROMBOSIS (See Guideline Notes 64,65,77)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: I81  
CPT: 37140,37180,37182,37183,49425-49429,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 218**  
Condition: TESTICULAR CANCER (See Guideline Notes 7,11,12,14,30)  
Treatment: BONE MARROW RESCUE AND TRANSPLANT  
ICD-10: C62.00-C62.92,D61.810,T86.5,Z48.290,Z51.11,Z52.000-Z52.098,Z52.3  
CPT: 36680,38204-38215,38230-38243,86825-86835,93792,93793,96377,96405,96406,96420-96440,96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S2142,S2150,S9537
- Line: 219**  
Condition: DENTAL CONDITIONS (E.G., PERIODONTAL DISEASE) (See Guideline Note 53)  
Treatment: BASIC PERIODONTICS  
ICD-10: K05.00-K05.20,K05.211-K05.6,K06.010-K06.1,K06.3  
HCPCS: D4210-D4212,D4341,D4342,D4910
- Line: 220**  
Condition: PULMONARY FIBROSIS (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: D86.0,D86.2,J84.01-J84.10,J84.111-J84.9,M30.1,M31.30-M31.31,M31.7,M32.13,M33.01,M33.11,M33.21,M33.91,M34.81,M35.02  
CPT: 31600,31601,31820,31825,32997,93792,93793,94002-94005,94640,94660-94668,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 221**  
Condition: DYSLIPIDEMIAS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: E78.00-E78.6  
CPT: 93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99195,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

**Line: 222**  
Condition: DISORDERS OF FLUID, ELECTROLYTE, AND ACID-BASE BALANCE (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY, DIALYSIS  
ICD-10: E72.20,E86.0-E86.9,E87.0-E87.6,E87.70-E87.8,E88.3,R57.1-R57.9,T81.10XA-T81.10XD,T81.19XA-T81.19XD,  
Z49.01-Z49.32  
CPT: 36818-36821,36832,36835,36838,36901-36909,49324-49326,49421,49422,49435,49436,90935-90947,90989-  
90997,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,  
99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,  
S9339,S9537

**Line: 223**  
Condition: OCCUPATIONAL LUNG DISEASES (See Guideline Notes 64,65,156)  
Treatment: MEDICAL THERAPY  
ICD-10: J60-J61,J62.0-J62.8,J63.0-J63.6,J64-J65,J66.0-J66.8,J67.0-J67.9,J68.0-J68.9,Z51.6  
CPT: 31600,86003,86008,86486,93792,93793,94002-94005,94640,94660-94668,95004,95018-95180,96150-96155,  
98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-  
99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0424-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,  
S9441

**Line: 224**  
Condition: DISEASES AND DISORDERS OF AORTIC VALVE (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL THERAPY  
ICD-10: I06.0-I06.9,I35.0-I35.9,I38-I39,Z79.01  
CPT: 33361-33413,33417,33496,33530,33620,33621,37246,37247,75557-75565,75573,92960-92971,92978-92998,  
93355,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,  
99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,  
G0508-G0511,G0513,G0514

**Line: 225**  
Condition: DISORDERS OF PARATHYROID GLAND; BENIGN NEOPLASM OF PARATHYROID GLAND; DISORDERS OF  
CALCIUM METABOLISM (See Guideline Notes 64,65,149)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: D35.1,D44.2,E20.0-E20.9,E21.0-E21.5,E83.50-E83.81,E89.2,N25.81  
CPT: 49185,60500-60512,93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,  
99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 226**  
Condition: ACUTE INFLAMMATION OF THE HEART DUE TO RHEUMATIC FEVER (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: I01.0-I01.9,I02.0  
CPT: 92960-92971,92978-92998,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-  
99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,  
G0508-G0511,G0513,G0514

**Line: 227**  
Condition: RUPTURED VISCUS (See Guideline Notes 64,65)  
Treatment: REPAIR  
ICD-10: K22.3,K62.7,K63.4,K66.1,K92.89,S27.812A-S27.812D,S27.813A-S27.813D,S27.818A-S27.818D,S27.819A-  
S27.819D  
CPT: 43300-43312,43405,44391,44602-44605,45317,45334,45382,45500,45560,45915,57268,57270,93792,93793,  
98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-  
99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

**Line: 228**  
Condition: **INTESTINAL MALABSORPTION** (See Coding Specification Below) (See Guideline Notes 64,65)  
Treatment: **MEDICAL THERAPY**  
ICD-10: K86.81,K90.0-K90.3,K90.49-K90.89,K91.2  
CPT: 93792,93793,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

ICD-10-CM code K90.89 (Other intestinal malabsorption) is included on this line only for chronic steatorrhea, exudative enteropathy, and protein-losing enteropathy.

**Line: 229**  
Condition: **FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES** (See Guideline Notes 64,65)  
Treatment: **SURGICAL TREATMENT**  
ICD-10: S02.2XXB-S02.2XXG,S02.30XA-S02.30XG,S02.31XA-S02.31XG,S02.32XA-S02.32XG,S02.400A-S02.400G,S02.401A-S02.401G,S02.402A-S02.402G,S02.40AA-S02.40AG,S02.40BA-S02.40BG,S02.40CA-S02.40CG,S02.40DA-S02.40DG,S02.40EA-S02.40EG,S02.40FA-S02.40FG,S02.411A-S02.411G,S02.412A-S02.412G,S02.413A-S02.413G,S02.42XA-S02.42XG,S02.600A-S02.600G,S02.601A-S02.601G,S02.602A-S02.602G,S02.609A-S02.609G,S02.610A-S02.610G,S02.611A-S02.611G,S02.612A-S02.612G,S02.620A-S02.620G,S02.621A-S02.621G,S02.622A-S02.622G,S02.630A-S02.630G,S02.631A-S02.631G,S02.632A-S02.632G,S02.640A-S02.640G,S02.641A-S02.641G,S02.642A-S02.642G,S02.650A-S02.650G,S02.651A-S02.651G,S02.652A-S02.652G,S02.66XA-S02.66XG,S02.670A-S02.670G,S02.671A-S02.671G,S02.672A-S02.672G,S02.69XA-S02.69XG,S02.80XA-S02.80XG,S02.81XA-S02.81XG,S02.82XA-S02.82XG,S02.92XA-S02.92XG,S04.011A-S04.011D,S04.012A-S04.012D,S04.019A-S04.019D,S04.02XA-S04.02XD,S04.031A-S04.031D,S04.032A-S04.032D,S04.039A-S04.039D,S04.10XA-S04.10XD,S04.11XA-S04.11XD,S04.12XA-S04.12XD,S04.20XA-S04.20XD,S04.21XA-S04.21XD,S04.22XA-S04.22XD,S04.30XA-S04.30XD,S04.31XA-S04.31XD,S04.32XA-S04.32XD,S04.40XA-S04.40XD,S04.41XA-S04.41XD,S04.42XA-S04.42XD,S04.50XA-S04.50XD,S04.51XA-S04.51XD,S04.52XA-S04.52XD,S04.60XA-S04.60XD,S04.61XA-S04.61XD,S04.62XA-S04.62XD,S04.70XA-S04.70XD,S04.71XA-S04.71XD,S04.72XA-S04.72XD,S04.811A-S04.811D,S04.812A-S04.812D,S04.819A-S04.819D,S04.891A-S04.891D,S04.892A-S04.892D,S04.899A-S04.899D,S04.9XXA-S04.9XXD  
CPT: 10121,11010-11012,12011-12018,20670,20680,20694,21085,21210,21215,21310-21470,30420,30450,31292-31294,92002-92014,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: D5988,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 230**  
Condition: **MALIGNANT MELANOMA OF SKIN** (See Guideline Notes 7,11,12,19,64,65,148)  
Treatment: **MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY**  
ICD-10: C43.0,C43.10-C43.9,D03.0,D03.10-D03.9,D61.810,G89.3,Z51.0,Z51.12,Z85.820  
CPT: 11600-11646,12001-12020,12031-13160,14350-15005,21011-21016,21552-21558,21632,21930-21936,22901-22905,23071-23078,24071-24079,25071-25078,26111-26118,27043-27049,27059,27075-27078,27327-27329,27337,27339,27364,27615-27619,27632,27634,28039-28047,32553,32674,38700-38780,49411,77014,77261-77295,77300-77307,77321-77370,77385-77387,77401-77432,77469,77470,78811-78816,81210,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,96904,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0219,G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

**Line: 231**  
Condition: **URINARY FISTULA** (See Guideline Notes 64,65)  
Treatment: **SURGICAL TREATMENT**  
ICD-10: N32.1-N32.2,N82.0-N82.1  
CPT: 44320,45820,50040,50045,50382-50389,50395,50432-50435,50520-50526,50688,50900-50930,50961,50970,50980,51800-51845,51880-51980,52234,53080,53085,53660,53661,57330,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

- Line: 232**  
Condition: MYCOBACTERIA, FUNGAL INFECTIONS, TOXOPLASMOSIS, AND OTHER OPPORTUNISTIC INFECTIONS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A31.2-A31.9,A42.0-A42.2,A42.89-A42.9,A43.0-A43.9,B37.1,B37.81-B37.82,B38.0-B38.7,B38.81-B38.9,B39.0-B39.9,B40.0-B40.7,B40.81-B40.9,B41.0-B41.9,B42.0-B42.7,B42.81-B42.9,B43.0-B43.9,B44.0-B44.7,B44.89-B44.9,B45.0-B45.7,B45.9,B46.0-B46.9,B47.0-B47.1,B48.0-B48.8,B49,B58.00-B58.1,B58.3,B58.81-B58.9,B59  
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 233**  
Condition: HYPOPLASTIC LEFT HEART SYNDROME  
Treatment: REPAIR  
ICD-10: Q23.4,Q25.29,Q25.40-Q25.42,Q25.49  
CPT: 33615-33622,33750,33764-33768,33924,33946-33966,33969,33984-33989,75557-75565,75573,93355,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 234**  
Condition: ADULT RESPIRATORY DISTRESS SYNDROME; ACUTE RESPIRATORY FAILURE; RESPIRATORY CONDITIONS DUE TO PHYSICAL AND CHEMICAL AGENTS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: B97.21,J18.2,J70.0,J70.2,J70.5,J80,J81.0,J95.821-J95.822,J96.00-J96.02,J96.20-J96.92  
CPT: 31600,31601,31610,31645,31646,31820,31825,33946-33966,33969,33984-33989,93792,93793,94002-94005,94640,94660-94668,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0424-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 235**  
Condition: ACUTE LYMPHOCYTIC LEUKEMIAS (ADULT) AND MULTIPLE MYELOMA (See Guideline Notes 7,11,12,64,65)  
Treatment: MEDICAL THERAPY, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C88.2-C88.3,C88.8-C88.9,C90.00-C90.32,C91.00-C91.02,D47.2,D61.810,E85.1-E85.4,E85.81-E85.9,G89.3,Z45.49,Z51.0,Z51.12  
CPT: 32553,36514,36516,49411,77014,77261-77295,77300-77307,77321-77370,77385-77387,77401-77431,77469,77470,79005-79445,93792,93793,95990,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537
- Line: 236**  
Condition: LIMB THREATENING VASCULAR DISEASE, INFECTIONS, AND VASCULAR COMPLICATIONS (See Guideline Notes 62,64,65,81)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: A48.0,E08.52,E09.52,E10.52,E11.52,E13.52,I70.211-I70.269,I70.311-I70.369,I70.411-I70.469,I70.511-I70.569,I70.611-I70.669,I70.711-I70.769,I70.92,I73.01-I73.1,I77.76-I77.77,I96,M60.000-M60.005,M60.011-M60.09,M72.6  
CPT: 10030,10060,11000-11057,15002,15003,23900-23921,23930,24900-24940,25028,25900-25931,26025,26030,26910-26952,26990,26991,27025,27290,27295,27301,27305,27590-27598,27603,27880-27889,28001-28003,28008,28150,28800-28825,29893,34101-34203,35081,35256,35302-35321,35351-35372,35500,35510-35671,35682-35686,35701-35761,35860,35875-35881,35903,36002,37184-37186,37220-37235,37246-37249,93792,93793,96150-96155,97605-97608,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 237**  
Condition: TETANUS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A33,A35  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

- Line: 238**  
Condition: ACUTE PROMYELOCYTIC LEUKEMIA (See Guideline Notes 7,11,12,16)  
Treatment: MEDICAL THERAPY, WHICH INCLUDES CHEMOTHERAPY, RADIATION AND RADIONUCLIDE THERAPY  
ICD-10: C92.00-C92.02,C92.40-C92.42,C95.00-C95.02,D61.810,G89.3,Z45.49,Z51.0,Z51.12  
CPT: 32553,38100,38120,38760,49411,77014,77261-77290,77295,77300,77306,77307,77321-77370,77385-77387,77401-77427,77469,77520-77525,81246,93792,93793,95990,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537
- Line: 239**  
Condition: CANCER OF OVARY (See Guideline Notes 7,11,12,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C56.1-C56.9,C57.00-C57.22,C79.60-C79.62,D39.10-D39.12,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.43  
CPT: 32553,38571-38573,38770,44110,44120,44140,49203-49205,49255,49327,49411,49412,49419,49422,57156,58150,58180-58210,58260,58541-58544,58548-58554,58570-58575,58660-58662,58720,58740,58925-58960,77014,77261-77290,77295,77300,77306,77307,77321-77370,77385-77387,77401-77417,77424-77427,77469,77470,77750,77790,79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537
- Line: 240**  
Condition: SHORT BOWEL SYNDROME - AGE 5 OR UNDER  
Treatment: INTESTINE AND INTESTINE/LIVER TRANSPLANT  
ICD-10: K55.30-K55.33,K91.2,P77.1-P77.9,T86.850-T86.859,Z48.23,Z48.288  
CPT: 44132,44135,44715-44721,47133-47147,86825-86835,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S2053
- Line: 241**  
Condition: CONDITIONS REQUIRING HEART-LUNG AND LUNG TRANSPLANTATION (See Guideline Note 151)  
Treatment: HEART-LUNG AND LUNG TRANSPLANT  
ICD-10: D86.0,E84.0,E84.8,I27.0,I27.89,J41.8,J43.0-J43.8,J47.0-J47.9,J60-J61,J62.0-J62.8,J63.0-J63.6,J65,J66.0-J66.8,J67.0-J67.9,J70.1,J70.3-J70.4,J84.111-J84.17,J84.81-J84.83,J84.841-J84.89,T27.1XXA-T27.1XXD,T27.5XXA-T27.5XXD,T86.810-T86.818,Z48.21,Z48.24,Z48.280  
CPT: 32850-32856,33930-33935,33946-33966,33969,33984-33989,81595,86825-86835,93792,93793,94640,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0424-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S2060,S2061
- Line: 242**  
Condition: ACUTE AND SUBACUTE NECROSIS OF LIVER; SPECIFIED INBORN ERRORS OF METABOLISM (E.G., MAPLE SYRUP URINE DISEASE, TYROSINEMIA)  
Treatment: LIVER TRANSPLANT  
ICD-10: D81.810,D84.1,E70.20-E70.29,E70.330-E70.331,E70.5-E70.9,E71.0,E71.110-E71.12,E72.10-E72.29,E72.52-E72.53,E72.8,E74.00-E74.09,E80.5,E83.00-E83.10,E83.110-E83.19,K72.00-K72.01,K73.1-K73.8,K76.2,T86.40-T86.49,Z48.23,Z52.6  
CPT: 47133-47147,86825-86835,93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 243**  
Condition: DERMATOLOGICAL PREMALIGNANT LESIONS AND CARCINOMA IN SITU (See Guideline Notes 64,65)  
Treatment: DESTRUCT/EXCISION/MEDICAL THERAPY  
ICD-10: D04.0,D04.10-D04.9,E70.30,E70.310-E70.329,E70.338-E70.39,L56.5,N48.0  
CPT: 11400-11446,11600-11646,13100-13160,14350,17000-17108,17260-17286,69110,69120,69300,93792,93793,96567,96573,96574,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

- Line: 244**  
Condition: PRIMARY ANGLE-CLOSURE GLAUCOMA (See Guideline Notes 64,65)  
Treatment: MEDICAL, SURGICAL AND LASER TREATMENT  
ICD-10: H21.81-H21.89,H40.031-H40.039,H40.061-H40.069,H40.20X0-H40.249  
CPT: 65860-65880,66150,66160,66179-66185,66250-66505,66625-66635,66761,66762,66990,76514,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 245**  
Condition: CORNEAL ULCER; SUPERFICIAL INJURY OF EYE AND ADNEXA (See Guideline Notes 64,65)  
Treatment: CONJUNCTIVAL FLAP; MEDICAL THERAPY  
ICD-10: E50.3,H16.001-H16.079,H16.231-H16.239,S00.251A-S00.251D,S00.252A-S00.252D,S00.259A-S00.259D,S05.00XA-S05.00XD,S05.01XA-S05.01XD,S05.02XA-S05.02XD  
CPT: 65275,65430,65600,65778-65782,67505,67515,68200,68360,68371,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 246**  
Condition: TORSION OF TESTIS (See Guideline Notes 64,65)  
Treatment: ORCHIECTOMY, REPAIR  
ICD-10: N44.00-N44.04  
CPT: 54512-54522,54600-54640,54660,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 247**  
Condition: LIFE-THREATENING EPISTAXIS (See Guideline Notes 64,65)  
Treatment: SEPTOPLASTY/REPAIR/CONTROL HEMORRHAGE  
ICD-10: R04.0  
CPT: 30520-30560,30620-30930,31238,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 248**  
Condition: RETAINED INTRAOCULAR FOREIGN BODY, MAGNETIC AND NONMAGNETIC (See Guideline Notes 64,65)  
Treatment: FOREIGN BODY REMOVAL  
ICD-10: H44.601-H44.799  
CPT: 65235-65265,66160,66840-66852,66940,67036,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 249**  
Condition: METABOLIC BONE DISEASE (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: M81.0-M81.8,M83.0-M83.9,M88.0-M88.1,M88.811-M88.9,M90.611-M90.69  
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 250**  
Condition: PARKINSON'S DISEASE (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: G20,G21.11-G21.9  
CPT: 61781,61782,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 251**  
Condition: CHRONIC PANCREATITIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: K86.0-K86.1,K86.89  
CPT: 43260-43265,43273-43278,47542,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

**Line: 252**  
Condition: MULTIPLE SCLEROSIS AND OTHER DEMYELINATING DISEASES OF CENTRAL NERVOUS SYSTEM (See Guideline Notes 64,65,95)  
Treatment: MEDICAL THERAPY  
ICD-10: G35,G36.0-G36.9,G37.0-G37.9,Z45.49,Z46.2  
CPT: 31600,31610,86711,90284,92081-92083,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 253**  
Condition: PSYCHOLOGICAL FACTORS AGGRAVATING PHYSICAL CONDITION (E.G., ASTHMA, CHRONIC GI CONDITIONS, HYPERTENSION) (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F54  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224-99226,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0019,H0023,H0032-H0038,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S9484,T1005

**Line: 254**  
Condition: ARTERIAL EMBOLISM/THROMBOSIS: ABDOMINAL AORTA, THORACIC AORTA (See Guideline Note 65)  
Treatment: SURGICAL TREATMENT  
ICD-10: I74.01-I74.19,I74.5-I74.8  
CPT: 33320-33335,33916,34001-34101,34201,34203,34839-34848,35081,35331,35363-35390,35535-35540,35560,35623-35638,35646,35647,35654,35681-35683,35691-35695,35741-35800,35875,35876,35901,36825,36830,37184-37186,37211,37213,37214,37236,37237,49324-49326,49421,49422,49435,49436,92960-92971,92978-92998,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 255**  
Condition: CHRONIC OSTEOMYELITIS (See Guideline Notes 6,64,65,100)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: M46.20-M46.28,M86.30,M86.311-M86.9  
CPT: 11000-11047,20005,20150,20690-20694,20930-20938,20955-20973,21620,21627,22532-22819,22840-22848,22853,22854,22859,23035,23105,23130,23170-23184,23220,23395,23935,24134-24147,24150,24152,24420,24498,25035,25085,25119,25145-25151,25210-25240,25320,25337,26034,26230-26236,26320,26951,26992,27070-27078,27187,27303,27360,27465-27468,27598,27607,27620,27640,27641,27745,27880-27888,28005,28120-28124,28800-28825,29075,29345,63045-63048,63081-63091,93792,93793,96150-96155,97012,97110-97124,97140-97168,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 256**  
Condition: MULTIPLE ENDOCRINE NEOPLASIA (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: E07.0,E31.1,E31.20-E31.23,Q92.0-Q92.5,Q92.62-Q92.8,Q93.0-Q93.2,Q95.2-Q95.3  
CPT: 60210-60240,60270,60271,60500-60512,60540,60545,60650,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 257**  
Condition: DEFORMITIES OF HEAD (See Guideline Notes 6,64,65,169)  
Treatment: CRANIOTOMY/CRANIECTOMY  
ICD-10: M95.2,Q67.4,Q75.0-Q75.9,Q87.0  
CPT: 11971,20660,20661,20665,21076,21077,21110,21120-21123,21137-21180,21182-21206,21210,21256-21275,21282,61312-61330,61340,61345,61550-61559,62115-62148,92507,92508,92521-92526,92607-92609,92633,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: D0364-D0367,D5915,D5919,D5924,D5928-D5931,D5933,D5992,D5993,D7111-D7240,D7280,D7283,D7940-D7955,D8010-D8693,G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9152



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

- Line: 258**  
Condition: DISEASES OF MITRAL, TRICUSPID, AND PULMONARY VALVES (See Guideline Notes 64,65)  
Treatment: VALVULOPLASTY, VALVE REPLACEMENT, MEDICAL THERAPY  
ICD-10: I01.1,I05.0-I05.9,I08.0,I08.8,I34.0-I34.9,I36.0-I36.9,I37.0-I37.9,I38-I39,I51.1-I51.2,Z79.01  
CPT: 33418-33465,33470-33496,33530,33620,33621,75557-75565,75573,92960-92971,92978-92998,93355,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 259**  
Condition: CANCER OF PENIS AND OTHER MALE GENITAL ORGANS (See Coding Specification Below) (See Guideline Notes 7,11,12,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C60.0-C60.9,C63.00-C63.9,D07.4,D07.60-D07.69,D40.8,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.45,Z85.48-Z85.49  
CPT: 11620-11626,17272-17276,32553,49327,49411,49412,52240,54065,54120-54135,54220,54230,54520-54535,54660,55150-55180,55920,58960,74445,77014,77261-77295,77300-77370,77385-77387,77402-77417,77424-77427,77469,77470,77600-77763,77770-77778,77790,79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542-96574,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537  
  
CPT 96567, 96573 and 96574 are included on this line only for pairing with ICD-10-CM D07.4.
- Line: 260**  
Condition: CANCER OF ENDOCRINE SYSTEM, EXCLUDING THYROID; CARCINOID SYNDROME (See Guideline Notes 7,11,12,19,25,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C37,C74.00-C74.92,C75.0-C75.9,C7A.00,C7A.091,C7A.094-C7A.098,C79.70-C79.72,D09.3-D09.8,D44.10-D44.12,D44.5-D44.7,D61.810,E34.0,G89.3,Z51.0,Z51.11-Z51.12  
CPT: 32553,32673,38204-38215,38230-38241,49411,60500,60512-60650,62165,64788,77014,77261-77295,77300-77307,77321-77370,77385-77387,77402-77432,77469,77470,78811-78816,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S2150,S9537
- Line: 261**  
Condition: MULTIPLE MYELOMA (See Guideline Notes 7,11,12,14)  
Treatment: BONE MARROW TRANSPLANT  
ICD-10: C88.0-C88.3,C88.8-C88.9,C90.00-C90.02,C90.20-C90.32,D47.2,D61.810,E85.1-E85.4,E85.81-E85.9,T86.01-T86.09,T86.5,Z48.290,Z52.000-Z52.098,Z52.3  
CPT: 36680,38204-38215,38230-38243,86825-86835,90284,93792,93793,96377,96405,96406,96420-96440,96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S2142,S2150,S9537
- Line: 262**  
Condition: CANCER OF RETROPERITONEUM, PERITONEUM, OMENTUM AND MESENTERY (See Guideline Notes 7,11,12,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C45.1,C48.0-C48.8,C49.A9,D48.3-D48.4,D61.810,G89.3,Z51.0,Z51.11-Z51.12  
CPT: 32553,39010,44820,44850,49203-49205,49255,49327,49411,49412,77014,77261-77290,77295,77300,77306-77370,77385-77387,77402-77417,77424-77427,77469,77470,77761-77763,77770-77790,79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

**Line: 263**  
Condition: CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS (See Coding Specification Below) (See Guideline Notes 7, 11, 12, 19, 64, 65, 142, 148, 174)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C33.C34.00-C34.92, C38.1-C38.8, C39.0-C39.9, C45.0, C7A.090, D02.1, D02.20-D02.22, D02.4, D38.1-D38.4, D61.810, G89.3, I87.1, J98.59, Z51.0, Z51.11-Z51.12, Z85.118-Z85.20  
CPT: 19260-19272, 21552, 21610, 22900, 31592, 31600, 31601, 31630, 31631, 31636-31646, 31770, 31775, 31785, 31786, 31820, 31825, 32320, 32440-32488, 32501-32550, 32552, 32553, 32650, 32662, 32663, 32666-32671, 32673-32701, 32900-32906, 32994, 38542, 38746, 38794, 39000-39220, 49411, 77014, 77261-77295, 77300-77370, 77373-77387, 77401-77470, 77761-77763, 77770-77790, 78811-78816, 81235, 93792, 93793, 96150-96155, 96377, 96405, 96406, 96420-96450, 96542, 96549, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0235, G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514, G6001-G6017, S9537

ICD-10-CM code I87.1 is included on this line for superior vena cava syndrome only.

**Line: 264**  
Condition: CONGESTIVE HEART FAILURE, CARDIOMYOPATHY, MALIGNANT ARRHYTHMIAS, AND COMPLEX CONGENITAL HEART DISEASE (See Guideline Notes 18, 64, 65, 70, 151)  
Treatment: CARDIAC TRANSPLANT; HEART/KIDNEY TRANSPLANT  
ICD-10: I13.11-I13.2, I25.110, I25.5, I40.0-I40.9, I42.0-I42.8, I47.2, I49.01-I49.02, I50.1, I50.20-I50.43, N18.5-N18.6, Q20.1-Q20.5, Q20.8, Q23.4, T86.21-T86.23, T86.290-T86.298, T86.31-T86.39, Z45.09, Z48.21, Z48.280-Z48.288  
CPT: 33620, 33621, 33940-33966, 33969, 33975-33993, 50300-50370, 50547, 75557-75565, 75573, 76776, 81595, 86825-86835, 92960-92971, 92978-92998, 93750, 93792-93798, 96150-96155, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0157-G0161, G0248-G0250, G0396, G0397, G0406-G0408, G0422, G0423, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514

**Line: 265**  
Condition: TRACHOMA (See Guideline Notes 64, 65)  
Treatment: MEDICAL THERAPY  
ICD-10: A71.0-A71.9, B55.1  
CPT: 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514

**Line: 266**  
Condition: ACUTE, SUBACUTE, CHRONIC AND OTHER TYPES OF IRIDOCYCLITIS (See Guideline Notes 64, 65)  
Treatment: MEDICAL THERAPY  
ICD-10: A18.54, A50.01, A50.30, A50.39, A51.43, A52.71, B58.00, B58.09, D86.83, H16.241-H16.249, H20.00, H20.011-H20.819, H20.9  
CPT: 67515, 68200, 76514, 92002-92014, 92018-92060, 92081-92136, 92225, 92226, 92230-92287, 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514

**Line: 267**  
Condition: DENTAL CONDITIONS (TIME SENSITIVE EVENTS) (See Guideline Notes 64, 65)  
Treatment: URGENT DENTAL SERVICES  
ICD-10: K00.6, K01.0-K01.1, K03.5, K03.81, K04.01-K04.99, K08.3, M27.2-M27.3, S02.5XXD-S02.5XXG  
CPT: 41000, 41800, 41806, 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99201-99215, 99281-99285, 99341-99378, 99381-99404, 99408-99449, 99487-99490, 99495-99498, 99605-99607  
HCPCS: D2910-D2921, D2940, D2950, D2970, D3120, D3220, D3222-D3240, D3351-D3353, D4920, D5410-D5422, D5850, D5851, D6930, D7111, D8695, D9120, D9951, G0248-G0250, G0396, G0397, G0463-G0467, G0490, G0511, G0513, G0514

**Line: 268**  
Condition: RICKETTSIAL AND OTHER ARTHROPOD-BORNE DISEASES (See Guideline Notes 64, 65)  
Treatment: MEDICAL THERAPY  
ICD-10: A44.0-A44.9, A68.0-A68.9, A69.20-A69.29, A75.0-A75.9, A77.1-A77.3, A77.40-A77.9, A78, A79.0-A79.1, A79.81-A79.9, A90-A91, A92.0-A92.2, A92.30-A92.9, A93.0-A93.8, A94, A95.0-A95.9, A98.0-A98.2, B33.1, B55.0, B55.2-B55.9, B60.0  
CPT: 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

**Line: 269**  
Condition: DIABETES INSIPIDUS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: E23.2  
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 270**  
Condition: ADVANCED DEGENERATIVE DISORDERS AND CONDITIONS OF GLOBE (See Guideline Notes 64,65)  
Treatment: ENUCLEATION  
ICD-10: H35.60-H35.63,H44.311-H44.399,H44.50,H44.511-H44.539,H44.811-H44.89  
CPT: 65091,65093,65105,65125-65175,67218,67560,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 271**  
Condition: CANCER OF BLADDER AND URETER (See Guideline Notes 7,11,12,64,65,148)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C66.1-C66.9,C67.0-C67.9,C79.11-C79.19,D09.0,D41.4,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.51  
CPT: 32553,38562,38564,38571-38573,38780,49327,49411,49412,50125,50220-50290,50340,50400,50405,50542-50548,50553,50572,50605,50650,50660,50693-50695,50780,50820-50840,50976,51530,51550-51597,51700,51720,52214-52250,52281,52282,52327,52332,52354,52355,52450,52500,53210-53220,55840,55920,57156,58960,77014,77261-77295,77300-77370,77385-77387,77402-77417,77424-77427,77469,77470,77761-77763,77770-77790,79005-79445,88120,88121,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

**Line: 272**  
Condition: TRAUMATIC AMPUTATION OF FOOT/FEET (COMPLETE)(PARTIAL) WITH AND WITHOUT COMPLICATION (See Guideline Notes 6,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: S98.011A-S98.011D,S98.012A-S98.012D,S98.019A-S98.019D,S98.021A-S98.021D,S98.022A-S98.022D,S98.029A-S98.029D,S98.311A-S98.311D,S98.312A-S98.312D,S98.319A-S98.319D,S98.321A-S98.321D,S98.322A-S98.322D,S98.329A-S98.329D,S98.911A-S98.911D,S98.912A-S98.912D,S98.919A-S98.919D,S98.921A-S98.921D,S98.922A-S98.922D,S98.929A-S98.929D  
CPT: 11010-11012,20838,27888,28800-28810,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 273**  
Condition: LEPROSY, YAWS, PINTA (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A30.0-A30.9,A31.1,A65,A66.0-A66.9,A67.0-A67.9,A69.8-A69.9  
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 274**  
Condition: RETINOPATHY OF PREMATURITY  
Treatment: CRYOSURGERY  
ICD-10: H35.101-H35.179,Q82.3  
CPT: 67101-67121,67227-67229,92002-92014,92018-92060,92081-92136,92225-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

- Line: 275**  
Condition: UROLOGIC INFECTIONS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A02.25,B37.0,B37.41-B37.49,B37.81,N11.8-N11.9,N12,N13.6,N30.00-N30.01,N30.20-N30.31,N30.80-N30.91,N39.0,N41.0,N45.1-N45.4,N49.0  
CPT: 50391,51100,51101,51700,52260,53450,54700,54860,54861,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 276**  
Condition: CANCER OF SKIN, EXCLUDING MALIGNANT MELANOMA (See Guideline Notes 7,11,12,16,19,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C4A.0,C4A.10-C4A.9,C44.00-C44.09,C44.101-C44.99,C46.0-C46.4,C46.50-C46.9,C79.2,D48.5,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.828  
CPT: 11000-11047,11400-11446,11600-11646,12001-12020,12031-13160,14350-15005,17000-17108,17260-17315,21011-21014,21016,21230,21235,21552-21558,21930-21936,22901-22905,23071-23078,24071-24079,25071-25078,26111-26118,27043-27048,27059,27327-27329,27337,27339,27364,27615-27619,27632,27634,28039-28047,32553,38542,38700-38745,38760,38765,40530-40654,49411,67840,67917,67950-67975,69110,69120,69145,69910,77014,77261-77295,77300-77307,77321-77370,77385-77387,77401-77432,77469,77470,77520-77525,78811-78816,79005-79445,92002-92014,92285,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,96904,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537
- Line: 277**  
Condition: OTHER PSYCHOTIC DISORDERS (See Guideline Notes 64,65,82)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F22-F24,F28-F29,F53  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99324-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005
- Line: 278**  
Condition: HYDROPS FETALIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: P56.0,P56.90-P56.99,P83.2  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 279**  
Condition: RETINAL DETACHMENT AND OTHER RETINAL DISORDERS (See Guideline Notes 64,65)  
Treatment: RETINAL REPAIR, VITRECTOMY  
ICD-10: E08.3521-E08.3549,E08.39,E09.3521-E09.3549,E09.39,E10.3521-E10.3549,E10.39,E11.3521-E11.3549,E11.39,E13.3521-E13.3549,E13.39,H31.401-H31.8,H33.001-H33.109,H33.191-H33.23,H33.40-H33.8,H43.00-H43.03,H43.311-H43.319,H44.2C1-H44.2C9,Z51.11  
CPT: 66990,67005-67113,67145,67208,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 280**  
Condition: BUDD-CHIARI SYNDROME, AND OTHER VENOUS EMBOLISM AND THROMBOSIS (See Guideline Notes 64,65,77,147)  
Treatment: THROMBECTOMY/LIGATION  
ICD-10: I82.0-I82.1,I82.210-I82.3,I82.601-I82.709,I82.721-I82.C29,I82.890-I82.91,Z79.01  
CPT: 34101,34401,34451-34530,35206-35226,35236-35256,35266-35286,35572,35681,35761-35840,35875,35876,35905,35907,37140,37160,37182,37183,37187-37193,37212-37214,37238,37239,37248,37249,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

- Line: 281**  
Condition: LIFE-THREATENING CARDIAC ARRHYTHMIAS (See Guideline Notes 49,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: I46.2-I46.9,I47.0,I47.2,I49.01-I49.02,I49.3,I97.120-I97.121,Z45.010-Z45.09,Z86.74  
CPT: 32160,33202-33251,33261-33264,33270-33273,33820,33967,92960-92971,92978-92998,93279-93284,93286-93289,93292-93296,93600-93656,93724,93745,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0448,G0463-G0467,G0490,G0508-G0511,G0513,G0514,K0606-K0609
- Line: 282**  
Condition: ANOREXIA NERVOSA (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F50.00-F50.02  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,97802-97804,98966-98969,99051,99060,99201-99239,99304-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005
- Line: 283**  
Condition: CHRONIC OBSTRUCTIVE PULMONARY DISEASE; CHRONIC RESPIRATORY FAILURE (See Guideline Notes 64,65,112)  
Treatment: MEDICAL THERAPY  
ICD-10: J41.1,J43.0-J43.9,J44.0-J44.9,J70.8-J70.9,J82,J96.10-J96.12,J98.4  
CPT: 31600,32480-32491,32663,32672,93792,93793,94002-94005,94640,94644-94668,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0424-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9346
- Line: 284**  
Condition: DISSECTING OR RUPTURED AORTIC ANEURYSM (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: I71.00-I71.1,I71.3,I71.5,I71.8,I77.72-I77.73  
CPT: 32110-32124,32820,33320-33335,33530,33860-33891,33916,34520,34701-34706,34709-34711,34839-34848,35081-35103,35306,35311,35331,35500-35515,35526,35531,35535-35540,35560,35563,35572,35601-35616,35626-35647,35663,35697,35820,35840,35870-35876,35905,35907,36825,36830,37236,37237,75956-75959,92960-92971,92978-92998,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 285**  
Condition: COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT (See Guideline Notes 6,62,64,65,90,105,131,147,164,170)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: C80.2,D64.81,D78.01,D78.11-D78.22,D89.810-D89.813,E36.01-E36.12,G04.01-G04.02,G04.31-G04.39,G89.12-G89.18,G96.0,G97.0,G97.2,G97.31-G97.32,G97.48-G97.82,H44.40,H44.431-H44.439,H59.111-H59.369,H95.21-H95.54,I77.79,I97.410-I97.89,J95.01-J95.72,J95.830-J95.89,J98.51,K68.11,K91.30-K91.32,K91.61-K91.83,K91.840-K91.841,K91.86,K91.870-K91.89,K94.01-K94.02,K94.11-K94.12,K94.21-K94.22,K94.31,K95.01-K95.89,L76.01-L76.22,M96.621-M96.831,M97.01XA-M97.01XD,M97.02XA-M97.02XD,M97.11XA-M97.11XD,M97.12XA-M97.12XD,M97.21XA-M97.21XD,M97.22XA-M97.22XD,M97.31XA-M97.31XD,M97.32XA-M97.32XD,M97.41XA-M97.41XD,M97.42XA-M97.42XD,M97.8XXA-M97.8XXD,M97.9XXA-M97.9XXD,N98.0,N99.0,N99.115,N99.510-N99.821,N99.89,O86.0,O90.0,O90.2,R50.84,T80.0XXA-T80.0XXD,T80.211A-T80.211D,T80.212A-T80.212D,T80.218A-T80.218D,T80.219A-T80.219D,T80.22XA-T80.22XD,T80.29XA-T80.29XD,T80.51XA-T80.51XD,T80.52XA-T80.52XD,T80.59XA-T80.59XD,T80.810A-T80.810D,T80.818A-T80.818D,T80.89XA-T80.89XD,T80.90XA-T80.90XD,T80.910A-T80.910D,T80.911A-T80.911D,T80.919A-T80.919D,T80.92XA-T80.92XD,T81.30XA-T81.30XD,T81.31XA-T81.31XD,T81.32XA-T81.32XD,T81.33XA-T81.33XD,T81.4XXA-T81.4XXD,T81.520A-T81.520D,T81.521A-T81.521D,T81.522A-T81.522D,T81.523A-T81.523D,T81.524A-T81.524D,T81.525A-T81.525D,T81.526A-T81.526D,T81.710A-T81.710D,T81.711A-T81.711D,T81.718A-T81.718D,T81.719A-T81.719D,T81.72XA-T81.72XD,T81.83XA-T81.83XD,T82.01XA-T82.01XD,T82.02XA-T82.02XD,T82.03XA-T82.03XD,T82.09XA-T82.09XD,T82.110A-T82.110D,T82.111A-T82.111D,T82.118A-T82.118D,T82.119A-T82.119D,T82.120A-T82.120D,T82.121A-T82.121D,T82.128A-T82.128D,T82.129A-T82.129D,T82.190A-T82.190D,T82.191A-T82.191D,T82.198A-T82.198D,T82.199A-T82.199D,T82.211A-T82.211D,T82.212A-T82.212D,T82.213A-T82.213D,T82.218A-T82.218D,T82.221A-T82.221D,T82.222A-T82.222D,T82.223A-T82.223D,T82.228A-T82.228D,T82.310A-T82.310D,T82.311A-T82.311D,T82.312A-T82.312D,T82.318A-T82.318D,T82.319A-T82.319D,T82.320A-T82.320D,T82.321A-T82.321D,T82.322A-T82.322D,



PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

T82.328A-T82.328D, T82.329A-T82.329D, T82.330A-T82.330D, T82.331A-T82.331D, T82.332A-T82.332D, T82.338A-T82.338D, T82.339A-T82.339D, T82.390A-T82.390D, T82.391A-T82.391D, T82.392A-T82.392D, T82.398A-T82.398D, T82.399A-T82.399D, T82.41XA-T82.41XD, T82.42XA-T82.42XD, T82.43XA-T82.43XD, T82.49XA-T82.49XD, T82.510A-T82.510D, T82.511A-T82.511D, T82.512A-T82.512D, T82.513A-T82.513D, T82.514A-T82.514D, T82.515A-T82.515D, T82.518A-T82.518D, T82.519A-T82.519D, T82.520A-T82.520D, T82.521A-T82.521D, T82.522A-T82.522D, T82.523A-T82.523D, T82.524A-T82.524D, T82.525A-T82.525D, T82.528A-T82.528D, T82.529A-T82.529D, T82.530A-T82.530D, T82.531A-T82.531D, T82.532A-T82.532D, T82.533A-T82.533D, T82.534A-T82.534D, T82.535A-T82.535D, T82.538A-T82.538D, T82.539A-T82.539D, T82.590A-T82.590D, T82.591A-T82.591D, T82.592A-T82.592D, T82.593A-T82.593D, T82.594A-T82.594D, T82.595A-T82.595D, T82.598A-T82.598D, T82.599A-T82.599D, T82.6XXA-T82.6XXD, T82.7XXA-T82.7XXD, T82.817A-T82.817D, T82.818A-T82.818D, 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T86.830-T86.99, T87.0X1-T87.2, T87.40-T87.54, T88.0XXA-T88.0XXD, T88.1XXA-T88.1XXD, T88.3XXA-T88.3XXD, T88.4XXA-T88.4XXD, Z45.010-Z45.09, Z45.49, Z47.32-Z47.33



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

**CPT:** 10030,10060,10061,10121-10180,11008,11042-11047,11982,12020,12021,13160,15002-15005,19328,20600-20611,20650,20670,20680,20693,20694,20975,21120,21501,21627,21750,22010,22015,22849-22852,22855,23334,23335,23472-23474,23800,23802,24160,24164,24430,24435,24800,24802,24925-24935,25109,25250,25251,25415,25420,25431-25446,25449,25907-26035,26060-26110,26115-26117,26121-26340,26350-26420,26428-26556,26565,26568-26910,26991,27030,27090,27091,27125-27138,27236,27265,27266,27284,27286,27301,27303,27310,27331,27448,27486-27488,27556,27580-27596,27703,27704,27786,27870,27882-27886,28715,29819,31290,31291,31613,31614,31750-31781,31800-31830,32120,33206-33215,33217-33223,33226-33249,33262-33264,33270-33273,33284,33361-33496,33510-33536,33768,33863,33968,33971,33974,33977,33978,33980-33983,34001-34203,34830,35188-35190,35301-35390,35500-35571,35583-35587,35601-35671,35700,35800-35907,36261,36514,36516,36818-36821,36825-36909,37182-37185,37192,37193,37197,37211,37212,37220-37239,37244-37249,37607,39000,39010,42960-42962,43255,43260-43265,43273-43278,43772-43774,43848,43860,43870,44120,44137,44312,44314,44340,44345,44640,45382,47542,47802,49020,49324,49325,49402-49407,49422,49423,50065,50135,50225,50370,50400,50405,50435,50525,50544,50727,50728,50830,50920-50940,51705,51710,51860-51925,52001,52310,54340-54352,54390,54406,54415,57287,57296,58301,61070,61880-61888,62160,62194,62225,62230,62256,62258,62272,62355,62365,63661-63664,63688,63707,63709,63744,63746,64569,64570,64585,64595,65150-65175,65710-65757,65920,67005-67028,67036-67043,75984,76514,92002-92014,92507,92508,92521-92526,92607-92609,92633,92928-92933,92937,92938,92943,92944,92978,92979,93590-93592,93644,93792,93793,97012,97110-97127,97140-97168,97530,97535,97542,97605-97608,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

**HCPCS:** G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0448,G0463-G0467,G0490,G0508-G0511,G0513-G0515,S9152

**Line: 286**  
**Condition:** CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS (See Guideline Notes 7,11,12,64,65)  
**Treatment:** MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
**ICD-10:** C51.0-C51.9,C52,C57.00-C57.9,D07.1-D07.2,D07.30-D07.39,D39.2-D39.9,D61.810,G89.3,R87.620-R87.629,Z51.0,Z51.11-Z51.12  
**CPT:** 11620-11626,32553,38562,38564,38571-38573,38760,49327,49411,49412,55920,56501,56515,56620-56640,57065,57106-57112,57156,57420,57421,57520,57530,57550,58150,58180-58260,58275,58285,58290,58541-58544,58548-58554,58570-58575,58661,58943-58960,77014,77261-77290,77295,77300-77370,77385-77387,77401-77417,77424-77427,77469,77470,77750-77763,77770-77790,79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
**HCPCS:** G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

**Line: 287**  
**Condition:** CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX (See Coding Specification Below) (See Guideline Notes 6,7,11,12,16,19,35,64,65)  
**Treatment:** MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
**ICD-10:** C00.0-C00.9,C01,C02.0-C02.9,C03.0-C03.9,C04.0-C04.9,C05.0-C05.9,C06.0-C06.2,C06.80-C06.9,C07,C08.0-C08.9,C09.0-C09.9,C10.0-C10.9,C11.0-C11.9,C12,C13.0-C13.9,C14.0-C14.8,C30.0-C30.1,C31.0-C31.9,C32.0-C32.9,C76.0,D02.0,D02.3,D11.0,D37.01-D37.02,D37.030-D37.09,D38.0,D38.5-D38.6,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.21-Z85.22,Z85.810-Z85.819  
**CPT:** 13132,13151,20962,21011-21014,21016,21552-21558,30117,30118,30520,31075-31230,31237,31300-31370,31380-31395,31540,31541,31572,31600,31601,31611,31820,31825,32553,38700-38724,40500-40530,40810-40816,40819,40845,41019,41110-41155,41820,41825-41827,41850,42104-42120,42280,42281,42410-42500,42826,42842-42845,42890-42950,43450,43496,49411,60220,69110,69150,69155,69502,77014,77261-77295,77300-77370,77385-77387,77401-77432,77469,77470,77520-77525,77750-77763,77770-77790,78811-78816,79005-79445,92507,92508,92521-92526,92607-92609,92633,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
**HCPCS:** D5983-D5985,D7440,D7441,D7920,D7981,G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9152,S9537

ICD-10-CM code D11.0 is included on this line only for parotid gland pleomorphic adenomas.

**Line: 288**  
**Condition:** OSTEOPETROSIS (See Guideline Notes 7,11,14)  
**Treatment:** BONE MARROW RESCUE AND TRANSPLANT  
**ICD-10:** D61.810,Q78.2,T86.01-T86.09,T86.5,Z48.290,Z52.000-Z52.098,Z52.3  
**CPT:** 36680,38204-38215,38230-38243,86825-86835,93792,93793,96150-96155,96377,96405,96406,96420-96440,96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
**HCPCS:** G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S2142,S2150,S9537



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

- Line: 289**  
Condition: CRUSH AND OTHER INJURIES OF DIGITS (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: S65.401A-S65.401D, S65.402A-S65.402D, S65.409A-S65.409D, S65.411A-S65.411D, S65.412A-S65.412D, S65.419A-S65.419D, S65.491A-S65.491D, S65.492A-S65.492D, S65.499A-S65.499D, S65.500A-S65.500D, S65.501A-S65.501D, S65.502A-S65.502D, S65.503A-S65.503D, S65.504A-S65.504D, S65.505A-S65.505D, S65.506A-S65.506D, S65.507A-S65.507D, S65.508A-S65.508D, S65.509A-S65.509D, S65.510A-S65.510D, S65.511A-S65.511D, S65.512A-S65.512D, S65.513A-S65.513D, S65.514A-S65.514D, S65.515A-S65.515D, S65.516A-S65.516D, S65.517A-S65.517D, S65.518A-S65.518D, S65.519A-S65.519D, S65.590A-S65.590D, S65.591A-S65.591D, S65.592A-S65.592D, S65.593A-S65.593D, S65.594A-S65.594D, S65.595A-S65.595D, S65.596A-S65.596D, S65.597A-S65.597D, S65.598A-S65.598D, S65.599A-S65.599D, S67.00XA-S67.00XD, S67.01XA-S67.01XD, S67.02XA-S67.02XD, S67.10XA-S67.10XD, S67.190A-S67.190D, S67.191A-S67.191D, S67.192A-S67.192D, S67.193A-S67.193D, S67.194A-S67.194D, S67.195A-S67.195D, S67.196A-S67.196D, S67.197A-S67.197D, S67.198A-S67.198D, S67.101A-S67.101D, S67.102A-S67.102D, S67.109A-S67.109D, S67.111A-S67.111D, S67.112A-S67.112D, S67.119A-S67.119D, S67.121A-S67.121D, S67.122A-S67.122D, S67.129A-S67.129D  
CPT: 11730, 11740, 11760, 20973, 25300, 25301, 29130, 35207, 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514
- Line: 290**  
Condition: ACUTE STRESS DISORDER (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F43.0, R45.7  
CPT: 90785, 90832-90840, 90846-90853, 90882, 90887, 93792, 93793, 98966-98969, 99051, 99060, 99201-99224, 99231-99239, 99324-99357, 99366, 99415, 99416, 99441-99449, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0406-G0408, G0410, G0411, G0425-G0427, G0459, G0463-G0467, G0469, G0470, G0508-G0511, G0513, G0514, H0004, H0023, H0032-H0038, H0045, H2010, H2012, H2013, H2021-H2023, H2027, H2032, H2033, S5151, S9125, S9484, T1005
- Line: 291**  
Condition: ADRENAL OR CUTANEOUS HEMORRHAGE OF FETUS OR NEONATE (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: P54.0, P54.4-P54.9  
CPT: 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99460-99463, 99468-99480, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514
- Line: 292**  
Condition: NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS (See Coding Specification Below) (See Guideline Notes 6,64,65,170)  
Treatment: MEDICAL AND SURGICAL TREATMENT (E.G., DURABLE MEDICAL EQUIPMENT AND ORTHOPEDIC PROCEDURE)  
ICD-10: A33, A50.40, A50.43, A50.45, A52.10-A52.19, A52.3, A81.00-A81.83, A87.1-A87.2, A88.8, A89, C70.0-C70.9, C71.0-C71.9, C72.0-C72.1, C72.20-C72.9, D33.9, D81.3, D81.5, E00.0-E00.9, E45, E70.0-E70.1, E70.20-E70.29, E70.330-E70.331, E70.5-E70.9, E71.0, E71.110-E71.548, E72.00, E72.02-E72.51, E72.59-E72.9, E74.00-E74.09, E74.20-E74.29, E75.00-E75.09, E75.11-E75.23, E75.240-E75.6, E76.01-E76.1, E76.210-E76.9, E77.0-E77.9, E78.70-E78.9, E79.1-E79.9, E80.0-E80.1, E80.20-E80.3, E83.00-E83.09, E88.2, E88.40-E88.49, E88.89, F01.50-F01.51, F03.90-F03.91, F06.1, F06.8, F07.89, F71-F79, F84.0-F84.3, F84.8, G04.1, G04.81-G04.91, G10, G11.0-G11.9, G12.0-G12.1, G12.21-G12.9, G13.1-G13.8, G14-G20, G21.0, G21.11-G21.9, G23.0-G23.9, G24.01, G24.1-G24.2, G24.8, G25.4-G25.5, G25.82, G25.9, G30.0-G30.8, G31.01-G31.83, G31.85-G31.9, G32.0, G32.81-G32.89, G35, G36.0-G36.9, G37.0-G37.9, G40.011-G40.019, G40.111-G40.119, G40.211-G40.219, G40.311-G40.319, G40.411-G40.419, G40.811, G40.89, G40.911-G40.919, G60.0-G60.8, G61.0-G61.1, G61.81-G61.89, G62.0-G62.2, G62.81-G62.89, G64, G71.0, G71.11-G71.8, G72.0-G72.3, G72.41-G72.89, G73.7, G80.0-G80.9, G81.00-G81.94, G82.20-G82.54, G83.0, G83.10-G83.9, G90.01-G90.1, G90.3-G90.4, G90.50, G90.511-G90.8, G91.0-G91.9, G92, G93.0-G93.1, G93.40-G93.81, G93.89, G94, G95.0, G95.11-G95.89, G97.0, G97.2, G97.31-G97.32, G97.48-G97.49, G97.61-G97.82, G98.0, G99.0-G99.8, H49.811-H49.819, I61.0-I61.9, I62.00-I62.9, I63.30, I63.311-I63.312, I63.319-I63.322, I63.329-I63.332, I63.339-I63.342, I63.349-I63.412, I63.419-I63.422, I63.429-I63.432, I63.439-I63.442, I63.449-I63.512, I63.519-I63.522, I63.529-I63.532, I63.539-I63.542, I63.549-I63.9, I67.3, I67.81-I67.83, I67.841-I67.89, I69.010-I69.018, I69.031-I69.090, I69.093, I69.110-I69.118, I69.131-I69.190, I69.193, I69.210-I69.218, I69.231-I69.290, I69.293, I69.310-I69.318, I69.331-I69.390, I69.393, I69.810-I69.818, I69.831-I69.890, I69.893, I69.910-I69.918, I69.931-I69.990, I69.993, I97.810-I97.821, M14.60, M14.611-M14.632, M14.641-M14.69, M24.50, M24.511-M24.576, M61.111-M61.112, M61.121-M61.122, M61.131-M61.132, M61.141-M61.142, M61.144-M61.145, M61.151-M61.152, M61.161-M61.162, M61.171-M61.172, M61.174-M61.175, M61.177-M61.178, M61.18-M61.19, M61.211-M61.212, M61.221-M61.222, M61.231-M61.232, M61.241-M61.242, M61.251-M61.252, M61.261-M61.262, M61.271-M61.272, M61.28-M61.29, M61.311-M61.312, M61.321-M61.322, M61.331-M61.332, M61.341-M61.342, M61.351-M61.352, M61.361-M61.362, M61.371-M61.372, M61.38-M61.39, M61.411-M61.412, M61.421-M61.422, M61.431-M61.432, M61.441-M61.442, M61.451-M61.452, M61.461-M61.462, M61.471-M61.472, M61.48-M61.49, M61.511-M61.512, M61.521-M61.522, M61.531-M61.532, M61.541-M61.542, M61.551-M61.552, M61.561-M61.562, M61.571-M61.572, M61.58-



PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

M61.59,M62.3,M62.411-M62.49,M62.511-M62.522,M62.531-M62.532,M62.541-M62.542,M62.551-M62.59,  
M62.89,M67.00-M67.02,P07.00-P07.39,P10.0-P10.9,P11.0,P11.2,P11.5-P11.9,P19.0-P19.9,P24.00-P24.21,  
P24.80-P24.9,P35.0-P35.9,P37.0-P37.9,P39.2,P50.0-P50.9,P51.0-P51.9,P52.0-P52.1,P52.21-P52.9,P54.1-P54.9,  
P55.1-P55.9,P56.0,P56.90-P56.99,P57.0,P91.2,P91.60-P91.63,P96.81,Q00.0-Q00.2,Q01.0-Q01.9,Q02,Q03.0-  
Q03.9,Q04.0-Q04.9,Q05.0-Q05.9,Q06.0-Q06.9,Q07.00-Q07.9,Q68.1,Q74.3,Q77.3,Q77.6,Q78.0-Q78.3,Q78.5-  
Q78.6,Q85.1,Q86.0-Q86.8,Q87.1-Q87.3,Q87.40,Q87.410-Q87.89,Q89.4-Q89.8,Q90.0-Q90.9,Q91.0-Q91.7,Q92.0-  
Q92.5,Q92.62-Q92.9,Q93.0-Q93.7,Q93.81-Q93.9,Q95.2-Q95.8,Q96.0-Q96.9,Q97.0-Q97.8,Q98.0-Q98.3,Q98.5-  
Q98.8,Q99.0-Q99.8,R41.4,R41.81,R53.2,R54,S06.370A-S06.370D,S06.810A-S06.810D,S06.811A-S06.811D,  
S06.812A-S06.812D,S06.813A-S06.813D,S06.814A-S06.814D,S06.815A-S06.815D,S06.816A-S06.816D,  
S06.817A-S06.819D,S06.820A-S06.820D,S06.821A-S06.821D,S06.822A-S06.822D,S06.823A-S06.823D,  
S06.824A-S06.824D,S06.825A-S06.825D,S06.826A-S06.826D,S06.827A-S06.829D,S06.890A-S06.890D,  
S06.891A-S06.891D,S06.892A-S06.892D,S06.893A-S06.893D,S06.894A-S06.894D,S06.895A-S06.895D,  
S06.896A-S06.896D,S06.897A-S06.899D,S06.9X0A-S06.9X0D,S06.9X1A-S06.9X1D,S06.9X2A-S06.9X2D,  
S06.9X3A-S06.9X3D,S06.9X4A-S06.9X4D,S06.9X5A-S06.9X5D,S06.9X6A-S06.9X6D,S06.9X7A-S06.9X9D,  
S14.0XXA-S14.0XXD,S14.101A-S14.101D,S14.102A-S14.102D,S14.103A-S14.103D,S14.104A-S14.104D,  
S14.105A-S14.105D,S14.106A-S14.106D,S14.107A-S14.107D,S14.108A-S14.108D,S14.109A-S14.109D,  
S14.111A-S14.111D,S14.112A-S14.112D,S14.113A-S14.113D,S14.114A-S14.114D,S14.115A-S14.115D,  
S14.116A-S14.116D,S14.117A-S14.117D,S14.118A-S14.118D,S14.119A-S14.119D,S14.121A-S14.121D,  
S14.122A-S14.122D,S14.123A-S14.123D,S14.124A-S14.124D,S14.125A-S14.125D,S14.126A-S14.126D,  
S14.127A-S14.127D,S14.128A-S14.128D,S14.129A-S14.129D,S14.131A-S14.131D,S14.132A-S14.132D,  
S14.133A-S14.133D,S14.134A-S14.134D,S14.135A-S14.135D,S14.136A-S14.136D,S14.137A-S14.137D,  
S14.138A-S14.138D,S14.139A-S14.139D,S14.141A-S14.141D,S14.142A-S14.142D,S14.143A-S14.143D,  
S14.144A-S14.144D,S14.145A-S14.145D,S14.146A-S14.146D,S14.147A-S14.147D,S14.148A-S14.148D,  
S14.149A-S14.149D,S14.151A-S14.151D,S14.152A-S14.152D,S14.153A-S14.153D,S14.154A-S14.154D,  
S14.155A-S14.155D,S14.156A-S14.156D,S14.157A-S14.157D,S14.158A-S14.158D,S14.159A-S14.159D,  
S14.2XXA-S14.2XXD,S14.3XXA-S14.3XXD,S24.0XXA-S24.0XXD,S24.101A-S24.101D,S24.102A-S24.102D,  
S24.103A-S24.103D,S24.104A-S24.104D,S24.109A-S24.109D,S24.111A-S24.111D,S24.112A-S24.112D,  
S24.113A-S24.113D,S24.114A-S24.114D,S24.119A-S24.119D,S24.131A-S24.131D,S24.132A-S24.132D,  
S24.133A-S24.133D,S24.134A-S24.134D,S24.139A-S24.139D,S24.141A-S24.141D,S24.142A-S24.142D,  
S24.143A-S24.143D,S24.144A-S24.144D,S24.149A-S24.149D,S24.151A-S24.151D,S24.152A-S24.152D,  
S24.153A-S24.153D,S24.154A-S24.154D,S24.159A-S24.159D,S24.2XXA-S24.2XXD,S34.01XA-S34.01XD,  
S34.02XA-S34.02XD,S34.101A-S34.101D,S34.102A-S34.102D,S34.103A-S34.103D,S34.104A-S34.104D,  
S34.105A-S34.105D,S34.109A-S34.109D,S34.111A-S34.111D,S34.112A-S34.112D,S34.113A-S34.113D,  
S34.114A-S34.114D,S34.115A-S34.115D,S34.119A-S34.119D,S34.121A-S34.121D,S34.122A-S34.122D,  
S34.123A-S34.123D,S34.124A-S34.124D,S34.125A-S34.125D,S34.129A-S34.129D,S34.131A-S34.131D,  
S34.132A-S34.132D,S34.139A-S34.139D,S34.21XA-S34.21XD,S34.22XA-S34.22XD,S34.3XXA-S34.3XXD,  
S34.4XXA-S34.4XXD,T40.0X1A-T40.0X1D,T40.0X2A-T40.0X2D,T40.0X3A-T40.0X3D,T40.0X4A-T40.0X4D,  
T40.1X1A-T40.1X1D,T40.1X2A-T40.1X2D,T40.1X3A-T40.1X3D,T40.1X4A-T40.1X4D,T40.2X1A-T40.2X1D,  
T40.2X2A-T40.2X2D,T40.2X3A-T40.2X3D,T40.2X4A-T40.2X4D,T40.3X1A-T40.3X1D,T40.3X2A-T40.3X2D,  
T40.3X3A-T40.3X3D,T40.3X4A-T40.3X4D,T40.4X1A-T40.4X1D,T40.4X2A-T40.4X2D,T40.4X3A-T40.4X3D,  
T40.4X4A-T40.4X4D,T40.5X1A-T40.5X1D,T40.5X2A-T40.5X2D,T40.5X3A-T40.5X3D,T40.5X4A-T40.5X4D,  
T40.601A-T40.601D,T40.602A-T40.602D,T40.603A-T40.603D,T40.604A-T40.604D,T40.691A-T40.691D,  
T40.692A-T40.692D,T40.693A-T40.693D,T40.694A-T40.694D,T40.7X1A-T40.7X1D,T40.7X2A-T40.7X2D,  
T40.7X3A-T40.7X3D,T40.7X4A-T40.7X4D,T40.8X1A-T40.8X1D,T40.8X2A-T40.8X2D,T40.8X3A-T40.8X3D,  
T40.8X4A-T40.8X4D,T40.901A-T40.901D,T40.902A-T40.902D,T40.903A-T40.903D,T40.904A-T40.904D,  
T40.991A-T40.991D,T71.111A-T71.111D,T71.112A-T71.112D,T71.113A-T71.113D,T71.114A-T71.114D,  
T71.121A-T71.121D,T71.122A-T71.122D,T71.123A-T71.123D,T71.124A-T71.124D,T71.131A-T71.131D,  
T71.132A-T71.132D,T71.133A-T71.133D,T71.134A-T71.134D,T71.141A-T71.141D,T71.143A-T71.143D,  
T71.144A-T71.144D,T71.151A-T71.151D,T71.152A-T71.152D,T71.153A-T71.153D,T71.154A-T71.154D,  
T71.161A-T71.161D,T71.162A-T71.162D,T71.163A-T71.163D,T71.164A-T71.164D,T71.191A-T71.191D,  
T71.192A-T71.192D,T71.193A-T71.193D,T71.194A-T71.194D,T71.20XA-T71.20XD,T71.21XA-T71.21XD,  
T71.221A-T71.221D,T71.222A-T71.222D,T71.223A-T71.223D,T71.224A-T71.224D,T71.231A-T71.231D,  
T71.232A-T71.232D,T71.233A-T71.233D,T71.234A-T71.234D,T71.29XA-T71.29XD,T71.9XXA-T71.9XXD,  
T74.4XXA-T74.4XXD,T75.01XA-T75.01XD,T75.09XA-T75.09XD,T75.1XXA-T75.1XXD,T75.4XXA-T75.4XXD,  
T78.00XA-T78.00XD,T78.01XA-T78.01XD,T78.02XA-T78.02XD,T78.03XA-T78.03XD,T78.04XA-T78.04XD,  
T78.05XA-T78.05XD,T78.06XA-T78.06XD,T78.07XA-T78.07XD,T78.08XA-T78.08XD,T78.09XA-T78.09XD,  
T78.3XXA-T78.3XXD,T78.8XXA-T78.8XXD,T79.0XXA-T79.0XXD,T79.4XXA-T79.4XXD,T79.6XXA-T79.6XXD,  
T88.2XXA-T88.2XXD,T88.51XA-T88.51XD,T88.6XXA-T88.6XXD,Z45.49,Z46.2,Z46.89,Z47.1  
CPT: 20550,20664,21610,23020,23800,23802,24149,24301-24331,24800,24802,25280,25290,25310-25332,25337,  
25800,25805,25830,26123,26125,26442,26460,26474,26490,27000-27006,27036,27097-27122,27140,27306,  
27307,27325,27326,27390-27400,27430,27435,27605,27606,27612,27676-27692,27705,27870,27871,28005,  
28010,28011,28130,28220-28234,28240,28300-28305,28307-28312,28705-28725,28737-28760,29405,29425,  
29895,29904-29907,32501,61215,61343,62161,62162,62320-62323,62350,62351,62360-62362,62367-62370,  
63600,63610,63650,63655,63685,64642-64647,64763,92531-92548,93792,93793,95873,95874,95990,97012,  
97018,97110-97124,97140-97168,97530,97535,97542,97760-97763,98925-98942,98966-98969,99051,99060,  
99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-  
99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,  
G0513,G0514,G9156

Spinal cord stimulation (63655-63688) is not included on this line when paired with ICD-10-CM category G90.5  
Complex regional pain syndrome/reflex sympathetic dystrophy. Chemodenervation with botulinum toxin injection



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(CPT 64642-64647) is included on this line for treatment of upper and lower limb spasticity (ICD-10-CM codes G24.02, G24.1, G35, G36.0, I69.03- I69.06 and categories G71, and G80-G83.) CPT codes 62320-3 are only included on Lines 71 and 292 for trials of antispasmodics in preparation for placement of a baclofen pump.

**Line: 293**  
Condition: ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER (See Guideline Notes 64,65,149)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: D18.09,K76.89,K83.4,Q44.0-Q44.7  
CPT: 43260-43265,43273-43278,47010,47400-47490,47533-47540,47542,47544,47554-47556,47564,47570,47600-47620,47701-47900,48548,49185,49324,49325,49405,49421,49422,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 294**  
Condition: CANCER OF BRAIN AND NERVOUS SYSTEM (See Guideline Notes 7,11,12,16,64,65,155)  
Treatment: LINEAR ACCELERATOR, MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C70.0-C70.9,C71.0-C71.9,C72.0-C72.1,C72.20-C72.9,C79.31-C79.32,C79.49,D42.0-D42.9,D43.0-D43.8,D61.810,G89.3,Z45.49,Z51.0,Z51.11-Z51.12,Z85.841-Z85.848  
CPT: 32553,49411,61107,61140,61210,61215,61312-61321,61500-61512,61516-61521,61530,61582,61583,61586,61592,61600-61608,61615,61616,61750,61751,61770-61783,61796-61800,62140-62148,62164,62165,62223,62272,63265,63275-63308,63615-63621,64784-64792,64802-64818,77014,77261-77295,77300-77372,77385-77387,77401-77432,77469,77470,77520-77763,77770-77790,79005-79445,92002-92014,93792,93793,95990,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: A4555,E0766,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

**Line: 295**  
Condition: APLASTIC ANEMIAS (See Guideline Note 7)  
Treatment: MEDICAL THERAPY  
ICD-10: D60.0-D60.9,D61.01-D61.3,D61.82-D61.9  
CPT: 38242,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9355

**Line: 296**  
Condition: CATARACT (See Guideline Notes 32,64,65)  
Treatment: EXTRACTION OF CATARACT  
ICD-10: E08.36,E09.36,E10.36,E11.36,E13.36,H25.011-H25.9,H26.001-H26.33,H26.8,H28,Q12.0-Q12.8,Z96.1  
CPT: 65770,66250,66682,66825-66984,66986,66990,67010,92002-92014,92018-92060,92081-92136,92225,92226,92230-92310,92314,92325-92342,92370,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 297**  
Condition: AFTER CATARACT  
Treatment: DISCISSION, LENS CAPSULE  
ICD-10: H26.40,H26.411-H26.499  
CPT: 66820-66830,66985-66990,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 298**  
Condition: FISTULA INVOLVING FEMALE GENITAL TRACT (See Guideline Notes 64,65)  
Treatment: CLOSURE OF FISTULA  
ICD-10: N82.0-N82.9  
CPT: 44625,44626,44660,46715,50650,50660,50930,51900,51920,57300-57330,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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**Line: 299**  
Condition: VITREOUS DISORDERS (See Guideline Notes 64,65)  
Treatment: VITRECTOMY  
ICD-10: H43.10-H43.23,H43.811-H43.829,Q14.0  
CPT: 67036-67043,67210,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 300**  
Condition: CLEFT PALATE AND/OR CLEFT LIP (See Guideline Notes 6,64,65,80)  
Treatment: EXCISION AND REPAIR VESTIBULE OF MOUTH, ORTHODONTICS  
ICD-10: Q30.2,Q35.1-Q35.9,Q36.0-Q36.9,Q37.0-Q37.9,Q38.0  
CPT: 00102,21076,21079,21080,21082,21083,30460,30462,30600,40500-40520,40650-40761,40810-40845,42145,42200-42281,92507,92508,92521-92526,92607-92609,92633,93792,93793,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: D5932,D5933,D5954-D5960,D5987,D5992,D5993,D7111-D7210,D7250,D7260,D7340,D7350,D7912,D8010-D8694,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9152

**Line: 301**  
Condition: GOUT (See Guideline Notes 6,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: M1A.00X0-M1A.9XX1,M10.00,M10.011-M10.9  
CPT: 20600-20611,93792,93793,96150-96155,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 302**  
Condition: PERTUSSIS AND DIPHTHERIA (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A36.0-A36.3,A36.81-A36.9,A37.00-A37.91  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 303**  
Condition: THROMBOCYTOPENIA (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: D69.1,D69.3,D69.41-D69.6,D75.82,D82.0  
CPT: 38100,38102,38120,90284,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 304**  
Condition: VIRAL PNEUMONIA (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: B01.2,B05.2,B06.81,J12.0-J12.3,J12.81-J12.9  
CPT: 31600,31601,31820,31825,93792,93793,94640,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 305**  
Condition: DISORDERS OF ARTERIES, OTHER THAN CAROTID OR CORONARY (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: I68.2,I75.81-I75.89,I76,I77.0,I77.2-I77.6,I77.89-I77.9,I79.1-I79.8,M31.8-M31.9,N28.0,Q27.1-Q27.2,Q27.31-Q27.39,Q27.8-Q27.9  
CPT: 34151,35256,35501-35515,35526,35531,35535-35540,35560,35563,35601-35616,35626-35646,35663,35761,37246,37247,37607,62294,63250-63252,63295,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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- Line: 306**  
Condition: PARALYTIC ILEUS (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: K56.0,K56.7  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 307**  
Condition: CIRRHOSIS OF LIVER OR BILIARY TRACT; BUDD-CHIARI SYNDROME; HEPATIC VEIN THROMBOSIS; INTRAHEPATIC VASCULAR MALFORMATIONS; CAROLI'S DISEASE (See Coding Specification Below)  
Treatment: LIVER TRANSPLANT, LIVER-KIDNEY TRANSPLANT  
ICD-10: I82.0,K65.2,K70.2,K70.30-K70.31,K74.0,K74.3-K74.5,K74.60-K74.69,K76.81,P59.1,P59.20-P59.29,P76.8-P76.9,P78.1,P78.81,P78.84,Q44.6,T86.40-T86.49,Z48.22-Z48.23,Z48.288,Z52.6  
CPT: 47133-47147,50300,50323-50365,76776,86825-86835,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514  
  
Liver-kidney transplant only included on this line for a documented diagnosis of Q44.6 (cystic disease of the liver).
- Line: 308**  
Condition: CHRONIC INFLAMMATORY DISORDER OF ORBIT (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: H05.10,H05.111-H05.129  
CPT: 67515,68200,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 309**  
Condition: CONGENITAL DISLOCATION OF HIP; COXA VARA AND VALGA (See Guideline Notes 6,64,65)  
Treatment: SURGICAL TREATMENT  
ICD-10: M21.859,Q65.00-Q65.89  
CPT: 27001-27006,27036,27140-27165,27179-27185,27256-27259,29305,29325,29861-29863,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 310**  
Condition: CORNEAL OPACITY AND OTHER DISORDERS OF CORNEA (See Guideline Notes 64,65,168)  
Treatment: KERATOPLASTY  
ICD-10: E50.4,H17.00-H17.13,H17.811-H17.89,H18.011-H18.13,H18.221-H18.229,H18.40,H18.411-H18.799,Q13.3-Q13.4  
CPT: 65286,65400,65436,65450,65710-65757,65772-65785,65920,66250,66825,66985-66990,68371,76514,92002-92014,92018-92060,92072-92136,92225,92226,92230-92310,92313-92342,92370,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 311**  
Condition: HEARING LOSS - AGE 5 OR UNDER (See Guideline Notes 51,64,65,103,143,154)  
Treatment: MEDICAL THERAPY INCLUDING HEARING AIDS, LIMITED SURGICAL THERAPY  
ICD-10: H72.00-H72.13,H72.2X1-H72.93,H83.3X1-H83.3X9,H90.0,H90.11-H90.8,H90.A11-H90.A32,H91.01-H91.09,H91.20-H91.3,H91.8X1-H91.93,H93.011-H93.099,H93.211-H93.249,H93.291-H93.8X9,H94.00-H94.83,S09.20XA-S09.20XD,S09.21XA-S09.21XD,S09.22XA-S09.22XD,Z01.12,Z46.1  
CPT: 42830,42835,69209,69210,69433,69436,69610-69646,69714-69718,92590-92595,92597,92626,92627,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514



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- Line: 312**  
Condition: GENDER DYSPHORIA/TRANSEXUALISM (See Guideline Note 127)  
Treatment: MEDICAL AND SURGICAL TREATMENT/PSYCHOTHERAPY  
ICD-10: F64.0-F64.9,Z87.890  
CPT: 17110,17111,17380,19303,19304,19316-19325,19340-19350,53415-53430,54120,54125,54520,54660,54690,55150-55180,55866,55970,55980,56620,56625,56800-56810,57106,57107,57110,57111,57291-57296,57335,57426,58150-58180,58260,58262,58275-58291,58353,58356,58541-58544,58550-58554,58563,58570-58573,58660,58661,58720,58940,90785,90832-90840,90846-90853,90882,90887,93792,93793,97110,97140,97161-97164,97530,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0396,G0397,G0459,G0463-G0467,G0469,G0470,G0490,G0511,G0513,G0514,H0004,H0023,H0032,H0034,H0035,H2010,H2014,H2027,H2032,H2033,S9484
- Line: 313**  
Condition: DISORDERS INVOLVING THE IMMUNE SYSTEM (See Guideline Notes 64,65,115,156)  
Treatment: MEDICAL THERAPY  
ICD-10: D69.0,D80.0-D80.9,D81.0-D81.4,D81.6-D81.7,D81.89-D81.9,D82.1-D82.9,D83.0-D83.9,D84.0-D84.9,D89.3,D89.40-D89.49,D89.810-D89.89,M04.1-M04.9,Q89.01-Q89.09,Z51.6  
CPT: 36514-36522,86003,86008,86486,90284,93792,93793,95004,95018-95180,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 314**  
Condition: CANCER OF ESOPHAGUS; BARRETT'S ESOPHAGUS WITH DYSPLASIA (See Guideline Notes 7,11,12,19,64,65,144)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C15.3-C15.9,C49.A1,D00.1,D61.810,G89.3,K22.710-K22.719,Z51.0,Z51.11-Z51.12,Z85.01  
CPT: 31540,31600,32553,38542,38720,38724,38794,43100-43124,43192,43195,43196,43201,43212-43214,43216-43229,43233,43248,43249,43266,43270,43286-43288,43340,43341,43360,43361,43496,44139-44147,44186,44204-44208,44213,44300,49411,49442,77014,77261-77295,77300-77307,77321-77370,77385-77387,77402-77427,77469,77470,77761-77763,77770-77790,78811-78816,79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0235,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537
- Line: 315**  
Condition: CANCER OF LIVER (See Guideline Notes 7,11,12,64,65,78)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C22.0-C22.9,C49.A9,C78.7,D37.6,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.05  
CPT: 32553,36260-36262,37243,37617,43260-43265,43274-43277,47120-47130,47370,47371,47380-47382,47533-47540,47542,47562,47600-47620,47711,47712,48150,49411,77014,77261-77295,77300-77370,77385-77387,77402-77417,77424-77432,77469,77470,79005-79440,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537
- Line: 316**  
Condition: CANCER OF PANCREAS (See Guideline Notes 7,11,12,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C25.0-C25.3,C25.7-C25.9,D01.7,D61.810,G89.3,Z51.0,Z51.11-Z51.12  
CPT: 32553,35251,35281,38747,43260-43265,43273-43278,44130,47542,47721,47741,47760,47785,48140-48155,49324,49325,49327,49411,49412,49421,49422,64680,77014,77261-77295,77300-77307,77321-77370,77385-77387,77402-77417,77424-77432,77469,77470,79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

**Line: 317**  
Condition: STROKE (See Guideline Notes 6,64,65,90,125)  
Treatment: MEDICAL THERAPY  
ICD-10: G89.0,I63.00,I63.011-I63.9,I67.0,I67.2,I67.6,I67.81-I67.83,I67.841-I67.89,Z79.01  
CPT: 34001,35301,35390,37195,37211,37213-37218,61322,61323,61343,61781,61782,61796-61800,77014,77261-77295,77300,77301,77336,77370-77372,77417,77423,77427-77432,92507,92508,92521-92526,92607-92609,92633,93792,93793,96150-96155,97012,97110-97127,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513-G0515,S9152

**Line: 318**  
Condition: PURULENT ENDOPHTHALMITIS (See Guideline Notes 64,65)  
Treatment: VITRECTOMY  
ICD-10: H21.331-H21.339,H33.121-H33.129,H44.001-H44.029,H44.121-H44.129,H44.19  
CPT: 65101,65800,66020,66030,67005-67036,67041-67043,67515,68200,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 319**  
Condition: FOREIGN BODY IN CORNEA AND CONJUNCTIVAL SAC (See Guideline Notes 64,65)  
Treatment: REMOVAL CONJUNCTIVAL FOREIGN BODY  
ICD-10: T15.00XA-T15.00XD,T15.01XA-T15.01XD,T15.02XA-T15.02XD,T15.10XA-T15.10XD,T15.11XA-T15.11XD,T15.12XA-T15.12XD,T15.80XA-T15.80XD,T15.81XA-T15.81XD,T15.82XA-T15.82XD,T15.90XA-T15.90XD,T15.91XA-T15.91XD,T15.92XA-T15.92XD  
CPT: 65205-65222,67938,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 320**  
Condition: OBESITY IN ADULTS AND CHILDREN; OVERWEIGHT STATUS IN ADULTS WITH CARDIOVASCULAR RISK FACTORS (See Guideline Notes 5,8,64,65)  
Treatment: BEHAVIORAL INTERVENTIONS INCLUDING INTENSIVE NUTRITIONAL AND PHYSICAL ACTIVITY COUNSELING; BARIATRIC SURGERY  
ICD-10: E66.01-E66.9,Z46.51,Z68.30-Z68.45,Z68.54,Z71.3,Z71.82  
CPT: 43644,43645,43771-43775,43846-43848,93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498  
HCPCS: G0248-G0250,G0396,G0397,G0447,G0463-G0467,G0473,G0490,G0511,G0513,G0514,S2083

**Line: 321**  
Condition: DERMATOLOGIC HEMANGIOMAS, COMPLICATED (See Guideline Note 13)  
Treatment: MEDICAL THERAPY  
ICD-10: D18.01  
CPT: 11400-11446,12031,12032,13100-13151,17106-17108,21011-21014,21552,21554,21931-21933,22901-22903,23071,23073,24071,24073,25071,25073,26111,26113,27043,27045,27337,27339,27632,27634,28039,28041,40500-40530,40810-40816,40820,41116,41826,42104-42107,42160,42808,69145,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 322**  
Condition: OTHER ANEURYSM OF PERIPHERAL ARTERY  
Treatment: SURGICAL TREATMENT  
ICD-10: I72.1,I72.4,I72.9  
CPT: 24900-24931,25900-25931,26910-26952,27590-27598,27880-27889,28800-28825,35001,35002,35011-35021,35141-35152,35572,35682,35683,35875,35876,35903,36002,37609,64802-64818,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

- Line: 323**  
Condition: SIALOADENITIS, ABSCESS, FISTULA OF SALIVARY GLANDS (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: K11.20-K11.4  
CPT: 40810-40816,42300-42340,42408,42410-42420,42440-42509,42600-42665,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: D7981-D7983,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 324**  
Condition: CYSTICERCOSIS, OTHER CESTODE INFECTION, TRICHINOSIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: B48.8,B68.1-B68.9,B69.0-B69.1,B69.81-B69.9,B70.0-B70.1,B71.0-B71.9,B75  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 325**  
Condition: NON-DISSECTING ANEURYSM WITHOUT RUPTURE (See Guideline Notes 64,65)  
Treatment: SURGICAL TREATMENT  
ICD-10: I71.2,I71.4,I71.6,I71.9,I72.0-I72.9,I77.810-I77.819,I79.0,Q25.43-Q25.44  
CPT: 33320-33335,33530,33860-33891,33916,34701-34711,34713,34715,34808-35081,35091,35102,35111-35152,35188,35301-35372,35500-35518,35526,35531,35535-35540,35560,35563,35572,35601-35671,35682,35683,35691-35697,35800-35840,35875,35876,35901,35905,35907,36002,36825,36830,37236,37237,37600-37606,37618,38100,75561-75565,75956-75959,92960-92971,92978-92998,93792-93798,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 326**  
Condition: SENSORINEURAL HEARING LOSS (See Guideline Note 31)  
Treatment: COCHLEAR IMPLANT  
ICD-10: H90.3,H90.41-H90.5,H90.A21-H90.A32,Z01.12,Z45.320-Z45.328  
CPT: 69930,92562-92565,92571-92577,92590,92591,92601-92604,92626-92633,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 327**  
Condition: FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION (See Coding Specification Below) (See Guideline Notes 45,57,64,65,145)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: N30.10-N30.11,N30.40-N30.41,N31.0-N31.2,N32.0,N32.3,N32.81,N35.010-N35.9,N36.44-N36.8,N39.490,N40.1,N43.40-N43.42,N48.30-N48.39,N50.1-N50.3,N53.11,N53.13-N53.19,N99.110-N99.114,N99.12,T19.0XXA-T19.0XXD,T19.1XXA-T19.1XXD,T19.4XXA-T19.4XXD,T19.8XXA-T19.8XXD,T19.9XXA-T19.9XXD,Z43.5-Z43.6,Z46.6  
CPT: 50706,50845,51040,51100-51102,51525,51700,51705-51715,51800-51845,51880-51980,52001,52214-52240,52260-52287,52305-52315,52355,52400,52450-52640,52648,52649,53020,53040,53400-53500,53600-53852,54115,54161,54220-54231,54240,54250,54420-54438,54520,54640,54660-54680,54700,54830-54861,54900,54901,55400,55520,55600-55680,55801,55821,55831,55862,55865,57220,57287,74445,93792,93793,97140,97161-97164,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514  
  
ICD-10-CM codes N40.1 and N40.3 are only included on this line when post-void residuals are at least 150 cc's.
- Line: 328**  
Condition: DISSEMINATED INTRAVASCULAR COAGULATION (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: D65  
CPT: 25900,25905,25915,25920,25927,26910-26952,27598,27880-27882,27888,27889,28800-28825,30150,54130,54135,69110,69120,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

**Line: 329**  
Condition: CANCER OF PROSTATE GLAND (See Guideline Notes 7,11,12,64,65,148)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C61,D07.5,D40.0,D61.810,G89.3,Z51.0,Z51.11-Z51.12,Z85.46  
CPT: 32553,38562,38564,38571-38573,38780,49327,49411,49412,51700,52234,52240,52281,52400,52450,52601-52640,52649,53600,53601,54520,54530,54660,55810-55866,58960,77014,77261-77295,77300-77370,77385-77387,77402-77417,77424-77427,77469,77470,77770-77790,79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0458,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537,S9560

**Line: 330**  
Condition: SYSTEMIC SCLEROSIS; SJOGREN'S SYNDROME (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: M34.0-M34.2,M34.81-M34.9,M35.01-M35.09  
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 331**  
Condition: ACUTE PROMYELOCYTIC LEUKEMIA  
Treatment: BONE MARROW TRANSPLANT  
ICD-10: C92.40-C92.42,D61.810,Z48.290,Z52.000-Z52.098,Z52.3  
CPT: 36680,38204-38215,38230-38243,86828-86835,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S2142,S2150,S9537

**Line: 332**  
Condition: CONDITIONS REQUIRING HYPERBARIC OXYGEN THERAPY (See Guideline Note 107)  
Treatment: HYPERBARIC OXYGEN  
ICD-10: E08.52,E08.621-E08.622,E09.52,E09.621-E09.622,E10.52,E10.621-E10.622,E11.52,E11.621-E11.622,E13.52,E13.621-E13.622,I70.361-I70.369,I70.461-I70.469,I70.561-I70.569,I70.661-I70.669,I70.761-I70.769,I96,K62.7,L59.8,L88,M27.2,M60.000-M60.005,M60.011-M60.09,M72.6,N30.40-N30.41,O08.0,O88.011-O88.03,Q52.9,S07.0XXA-S07.0XXD,S07.1XXA-S07.1XXD,S07.8XXA-S07.8XXD,S07.9XXA-S07.9XXD,S17.0XXA-S17.0XXD,S17.8XXA-S17.8XXD,S17.9XXA-S17.9XXD,S38.001A-S38.001D,S38.002A-S38.002D,S38.01XA-S38.01XD,S38.02XA-S38.02XD,S38.03XA-S38.03XD,S38.1XXA-S38.1XXD,S38.211A-S38.211D,S38.212A-S38.212D,S38.221A-S38.221D,S38.222A-S38.222D,S38.231A-S38.231D,S38.232A-S38.232D,S38.3XXA-S38.3XXD,S47.1XXA-S47.1XXD,S47.2XXA-S47.2XXD,S47.9XXA-S47.9XXD,S57.00XA-S57.00XD,S57.01XA-S57.01XD,S57.02XA-S57.02XD,S57.80XA-S57.80XD,S57.81XA-S57.81XD,S57.82XA-S57.82XD,S67.00XA-S67.00XD,S67.01XA-S67.01XD,S67.02XA-S67.02XD,S67.10XA-S67.10XD,S67.190A-S67.190D,S67.191A-S67.191D,S67.192A-S67.192D,S67.193A-S67.193D,S67.194A-S67.194D,S67.195A-S67.195D,S67.196A-S67.196D,S67.197A-S67.197D,S67.198A-S67.198D,S67.20XA-S67.20XD,S67.21XA-S67.21XD,S67.22XA-S67.22XD,S67.30XA-S67.30XD,S67.31XA-S67.31XD,S67.32XA-S67.32XD,S67.40XA-S67.40XD,S67.41XA-S67.41XD,S67.42XA-S67.42XD,S67.90XA-S67.90XD,S67.91XA-S67.91XD,S67.92XA-S67.92XD,S77.00XA-S77.00XD,S77.01XA-S77.01XD,S77.02XA-S77.02XD,S77.10XA-S77.10XD,S77.11XA-S77.11XD,S77.12XA-S77.12XD,S77.20XA-S77.20XD,S77.21XA-S77.21XD,S77.22XA-S77.22XD,S87.00XA-S87.00XD,S87.01XA-S87.01XD,S87.02XA-S87.02XD,S87.80XA-S87.80XD,S87.81XA-S87.81XD,S87.82XA-S87.82XD,S97.00XA-S97.00XD,S97.01XA-S97.01XD,S97.02XA-S97.02XD,S97.101A-S97.101D,S97.102A-S97.102D,S97.109A-S97.109D,S97.111A-S97.111D,S97.112A-S97.112D,S97.119A-S97.119D,S97.121A-S97.121D,S97.122A-S97.122D,S97.129A-S97.129D,S97.80XA-S97.80XD,S97.81XA-S97.81XD,S97.82XA-S97.82XD,T57.1X1A-T57.1X1D,T57.1X2A-T57.1X2D,T57.1X3A-T57.1X3D,T57.1X4A-T57.1X4D,T57.3X1A-T57.3X1D,T57.3X2A-T57.3X2D,T57.3X3A-T57.3X3D,T57.3X4A-T57.3X4D,T58.01XA-T58.01XD,T58.02XA-T58.02XD,T58.03XA-T58.03XD,T58.04XA-T58.04XD,T58.11XA-T58.11XD,T58.12XA-T58.12XD,T58.13XA-T58.13XD,T58.14XA-T58.14XD,T58.2X1A-T58.2X1D,T58.2X2A-T58.2X2D,T58.2X3A-T58.2X3D,T58.2X4A-T58.2X4D,T58.8X1A-T58.8X1D,T58.8X2A-T58.8X2D,T58.8X3A-T58.8X3D,T58.8X4A-T58.8X4D,T58.91XA-T58.91XD,T58.92XA-T58.92XD,T58.93XA-T58.93XD,T58.94XA-T58.94XD,T59.0X1A-T59.0X1D,T59.0X2A-T59.0X2D,T59.0X3A-T59.0X3D,T59.0X4A-T59.0X4D,T59.1X1A-T59.1X1D,T59.1X2A-T59.1X2D,T59.1X3A-T59.1X3D,T59.1X4A-T59.1X4D,T59.2X1A-T59.2X1D,T59.2X2A-T59.2X2D,T59.2X3A-T59.2X3D,T59.2X4A-T59.2X4D,T59.3X1A-T59.3X1D,T59.3X2A-T59.3X2D,T59.3X3A-T59.3X3D,T59.3X4A-T59.3X4D,T59.4X1A-T59.4X1D,T59.4X2A-T59.4X2D,T59.4X3A-T59.4X3D,T59.4X4A-T59.4X4D,T59.5X1A-T59.5X1D,T59.5X2A-T59.5X2D,T59.5X3A-T59.5X3D,T59.5X4A-T59.5X4D,T59.6X1A-T59.6X1D,T59.6X2A-T59.6X2D,T59.6X3A-T59.6X3D,T59.6X4A-T59.6X4D,T59.7X1A-T59.7X1D,T59.7X2A-T59.7X2D,T59.7X3A-T59.7X3D,T59.7X4A-T59.7X4D,T59.811A-T59.811D,T59.812A-T59.812D,T59.813A-T59.813D,T59.814A-T59.814D,T59.891A-T59.891D,T59.892A-T59.892D,T59.893A-T59.893D,T59.894A-T59.894D,T59.91XA-T59.91XD,T59.92XA-T59.92XD,T59.93XA-T59.93XD,T59.94XA-T59.94XD,T66.XXXA-T66.XXXD,T70.3XXA-T70.3XXD,T79.0XXA-T79.0XXD,T79.A0XA-T79.A0XD,T79.A11A-T79.A11D,T79.A12A-T79.A12D,T79.A19A-T79.A19D,T79.A21A-T79.A21D,T79.A22A-T79.A22D,T79.A29A-T79.A29D,T79.A3XA-T79.A3XD,T79.A9XA-T79.A9XD,T80.0XXA-T80.0XXD,T82.898A-T82.898D,T82.9XXA-T82.9XXD,T83.89XA-T83.89XD,T83.9XXA-T83.9XXD,T84.89XA-T84.89XD,T84.9XXA-T84.9XXD,



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T85.9XXA-T85.9XXD,T86.820-T86.829  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99183,99184,99201-99239,99281-99285,99291-99404,  
99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0277,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,  
G0514

**Line: 333**  
Condition: BENIGN CEREBRAL CYSTS  
Treatment: DRAINAGE  
ICD-10: B69.0,G93.0,G96.12-G96.19,M25.08  
CPT: 61120,61150,61151,61314-61316,61516,61522,61524,61781,61782,62223,93792,93793,98966-98969,99051,  
99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,  
99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 334**  
Condition: ALCOHOLIC FATTY LIVER OR ALCOHOLIC HEPATITIS, CIRRHOSIS OF LIVER (See Guideline Notes  
64,65,77)  
Treatment: MEDICAL THERAPY  
ICD-10: K70.0,K70.10-K70.9,K71.3-K71.4,K71.50-K71.7,K72.10-K72.91,K74.0,K74.3-K74.5,K74.60-K74.69,K76.1,K76.6,  
K76.89  
CPT: 37182,37183,93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-  
99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 335**  
Condition: SCLERITIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A18.51,A50.01,A50.30,A50.39,A51.43,A52.71,B58.00,B58.09,H15.001-H15.099,H15.121-H15.89  
CPT: 66130,66220-66250,67250,67255,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,  
93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,  
99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 336**  
Condition: RUBEOSIS AND OTHER DISORDERS OF THE IRIS (See Guideline Notes 64,65)  
Treatment: LASER SURGERY  
ICD-10: H21.1X1-H21.1X9,H21.40-H21.43,H21.501-H21.569,Q13.1  
CPT: 65870,65875,66170,66680,66682,66720,67228,67500,76514,92002-92014,92018-92060,92081-92136,92225,  
92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,  
99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 337**  
Condition: WOUND OF EYE GLOBE (See Guideline Notes 64,65)  
Treatment: SURGICAL REPAIR  
ICD-10: S05.20XA-S05.20XD,S05.21XA-S05.21XD,S05.22XA-S05.22XD,S05.30XA-S05.30XD,S05.31XA-S05.31XD,  
S05.32XA-S05.32XD,S05.50XA-S05.50XD,S05.51XA-S05.51XD,S05.52XA-S05.52XD,S05.60XA-S05.60XD,  
S05.61XA-S05.61XD,S05.62XA-S05.62XD,S05.70XA-S05.70XD,S05.71XA-S05.71XD,S05.72XA-S05.72XD,  
S05.8X1A-S05.8X1D,S05.8X2A-S05.8X2D,S05.8X9A-S05.8X9D,S05.90XA-S05.90XD,S05.91XA-S05.91XD,  
S05.92XA-S05.92XD  
CPT: 65105,65235-65273,65280,65285,65290,66680,92002-92014,92018-92060,92081-92136,92225,92226,92230-  
92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,  
99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 338**  
Condition: ACUTE NECROSIS OF LIVER (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: K71.0,K71.10-K71.2,K71.8-K71.9,K72.00-K72.01,K75.2-K75.3,K75.89,K76.2,K76.89  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-  
99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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- Line: 339**  
Condition: CHRONIC KIDNEY DISEASE (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY INCLUDING DIALYSIS  
ICD-10: B52.0,E08.21-E08.29,E09.21-E09.29,E10.21-E10.29,E11.21-E11.29,E13.21-E13.29,E88.3,I12.0-I12.9,N02.0-N02.9,N03.0-N03.9,N04.0-N04.9,N05.2-N05.9,N06.0-N06.9,N07.0-N07.9,N08,N14.0-N14.4,N15.0,N15.8-N15.9,N16,N18.1-N18.5,N18.9,N25.0-N25.1,N25.89,N26.1,N26.9,N27.0-N27.9,N28.9,N29,Z49.01-Z49.32  
CPT: 36514,36516,36800-36821,36825-36838,36901-36909,49324-49326,49421,49422,49435,49436,90935-90947,90989-90997,93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9339,S9355,S9537
- Line: 340**  
Condition: HEREDITARY HEMORRHAGIC TELANGIECTASIA (See Guideline Note 65)  
Treatment: EXCISION  
ICD-10: I78.0  
CPT: 11400-11426,45382,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 341**  
Condition: RHEUMATIC FEVER (See Guideline Notes 6,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: I00,I02.9  
CPT: 93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 342**  
Condition: OTHER AND UNSPECIFIED ANTERIOR PITUITARY HYPERFUNCTION, BENIGN NEOPLASM OF THYROID GLAND AND OTHER ENDOCRINE GLANDS (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES RADIATION THERAPY  
ICD-10: D34,D35.00-D35.02,D35.2-D35.9,E16.3-E16.9,E22.1-E22.9,E23.3,E34.4,G89.3,Z51.0  
CPT: 32553,48140,48155,49411,60200-60240,60270,60271,60512,60600-60650,61548,62100,77338,77402,79005-79445,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 343**  
Condition: DENTAL CONDITIONS (E.G., CARIES, FRACTURED TOOTH) (See Guideline Notes 91,123)  
Treatment: BASIC RESTORATIVE (E.G., COMPOSITE RESTORATIONS FOR ANTERIOR TEETH, AMALGAM RESTORATIONS FOR POSTERIOR TEETH)  
ICD-10: K02.3,K02.51-K02.9,K03.2,K03.89,K08.530-K08.539  
HCPCS: D1354,D2140-D2394,D2930-D2933,D2941,D2950,D2951,D2954,D2957,D2980,D6980
- Line: 344**  
Condition: DENTAL CONDITIONS (E.G., SEVERE CARIES, INFECTION) (See Guideline Notes 34,48)  
Treatment: ORAL SURGERY (I.E., EXTRACTIONS AND OTHER INTRAORAL SURGICAL PROCEDURES)  
ICD-10: E08.630-E08.638,E09.630-E09.638,E10.630-E10.638,E11.630-E11.638,E13.630-E13.638,K02.3,K02.51-K02.9  
CPT: 41870,41872  
HCPCS: D6096,D6100,D7210-D7251,D7310-D7321,D7450,D7451,D7465,D7471,D7540,D7550,D7960,D7963,D7971,D9930
- Line: 345**  
Condition: NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS (See Guideline Notes 6,64,65,90)  
Treatment: MEDICAL THERAPY  
ICD-10: A33,A50.40,A50.43,A50.45,A52.10,A52.12-A52.15,A52.17-A52.19,A52.3,A81.00-A81.83,A87.1-A87.2,A88.8,A89,C32.8-C32.9,C70.0-C70.9,C71.0-C71.9,C72.0-C72.1,C72.20-C72.9,D33.9,D81.3,D81.5,E00.0-E00.9,E45,E70.0-E70.1,E70.20-E70.29,E70.330-E70.331,E70.8-E70.9,E71.0,E71.110-E71.548,E72.00,E72.02-E72.51,E72.59-E72.9,E74.00-E74.09,E74.20-E74.29,E75.00-E75.09,E75.11-E75.23,E75.240-E75.6,E76.01-E76.1,E76.210-E76.9,E77.0-E77.9,E78.70-E78.9,E79.1-E79.9,E80.0-E80.1,E80.20-E80.3,E83.00-E83.09,E88.2,E88.40-E88.49,E88.89,F01.50-F01.51,F03.90-F03.91,F06.1,F06.8,F07.89,F70-F79,F80.0-F80.4,F80.81-F80.89,F84.0-F84.3,F84.8,F98.5,G04.1,G04.81-G04.91,G10,G11.0-G11.4,G11.9,G12.0-G12.1,G12.21-G12.9,G13.1-G13.8,G14-G20,G21.0,G21.11-G21.9,G23.0-G23.9,G24.1-G24.2,G24.8,G25.4-G25.5,G25.82,G25.9,G30.0-G30.8,G31.01-G31.83,G31.85-G31.9,G32.0,G32.81-G32.89,G35,G36.0-G36.9,G37.0-G37.9,G40.011-G40.019,G40.111-G40.119,



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G40.211-G40.219,G40.311-G40.319,G40.411-G40.419,G40.811,G40.89,G40.911-G40.919,G60.0-G60.8,G61.0-G61.1,G61.81-G61.89,G62.0-G62.2,G62.81-G62.89,G64,G71.0,G71.11-G71.8,G72.0-G72.3,G72.41-G72.89,G73.7,G80.0-G80.9,G81.00-G81.94,G82.20-G82.54,G83.0,G83.30-G83.9,G90.01-G90.1,G90.3-G90.4,G91.0-G91.9,G92,G93.0-G93.1,G93.40-G93.81,G93.89,G94,G95.0,G95.11-G95.29,G95.89,G97.0,G97.2,G97.31-G97.32,G97.48-G97.49,G97.61-G97.82,G99.0-G99.8,H49.811-H49.819,H93.25,I61.0-I61.9,I62.00-I62.9,I63.30,I63.311-I63.312,I63.319-I63.322,I63.329-I63.332,I63.339-I63.342,I63.349-I63.412,I63.419-I63.422,I63.429-I63.432,I63.439-I63.442,I63.449-I63.512,I63.519-I63.522,I63.529-I63.532,I63.539-I63.542,I63.549-I63.9,I67.3,I67.81-I67.83,I67.841-I67.89,I69.010-I69.018,I69.020-I69.028,I69.051-I69.090,I69.092,I69.110-I69.118,I69.120-I69.128,I69.151-I69.190,I69.192,I69.210-I69.218,I69.220-I69.228,I69.251-I69.290,I69.292,I69.310-I69.318,I69.320-I69.328,I69.351-I69.390,I69.392,I69.810-I69.818,I69.820-I69.828,I69.851-I69.890,I69.892,I69.910-I69.918,I69.920-I69.928,I69.951-I69.990,I69.992,I97.810-I97.821,M62.3,M62.58-M62.59,M62.89,P07.00-P07.39,P10.0-P10.9,P11.0,P11.2,P11.5-P11.9,P19.0-P19.9,P24.00-P24.21,P24.80-P24.9,P35.0-P35.9,P37.0-P37.9,P39.2,P50.0-P50.9,P51.0-P51.9,P52.0-P52.1,P52.21-P52.9,P54.1-P54.9,P55.1-P55.9,P56.0,P56.90-P56.99,P57.0,P91.2,P91.60-P91.63,P96.81,Q00.0-Q00.2,Q01.0-Q01.9,Q02,Q03.0-Q03.9,Q04.0-Q04.9,Q05.0-Q05.9,Q06.0-Q06.9,Q07.00-Q07.9,Q74.3,Q77.3,Q77.6,Q78.0-Q78.3,Q78.5-Q78.6,Q85.1,Q86.0-Q86.8,Q87.1-Q87.3,Q87.40,Q87.410-Q87.89,Q89.4-Q89.8,Q90.0-Q90.9,Q91.0-Q91.7,Q92.0-Q92.5,Q92.62-Q92.9,Q93.0-Q93.7,Q93.81-Q93.9,Q95.2-Q95.8,Q96.0-Q96.9,Q97.0-Q97.8,Q98.0-Q98.3,Q98.5-Q98.8,Q99.0-Q99.8,R13.10-R13.19,R41.4,R41.81,R53.2,R54,S06.370A-S06.370D,S06.810A-S06.810D,S06.811A-S06.811D,S06.812A-S06.812D,S06.813A-S06.813D,S06.814A-S06.814D,S06.815A-S06.815D,S06.816A-S06.816D,S06.817A-S06.819D,S06.820A-S06.820D,S06.821A-S06.821D,S06.822A-S06.822D,S06.823A-S06.823D,S06.824A-S06.824D,S06.825A-S06.825D,S06.826A-S06.826D,S06.827A-S06.829D,S06.890A-S06.890D,S06.891A-S06.891D,S06.892A-S06.892D,S06.893A-S06.893D,S06.894A-S06.894D,S06.895A-S06.895D,S06.896A-S06.896D,S06.897A-S06.899D,S06.9X0A-S06.9X0D,S06.9X1A-S06.9X1D,S06.9X2A-S06.9X2D,S06.9X3A-S06.9X3D,S06.9X4A-S06.9X4D,S06.9X5A-S06.9X5D,S06.9X6A-S06.9X6D,S06.9X7A-S06.9X9D,S14.0XXA-S14.0XXD,S14.101A-S14.101D,S14.102A-S14.102D,S14.103A-S14.103D,S14.104A-S14.104D,S14.105A-S14.105D,S14.106A-S14.106D,S14.107A-S14.107D,S14.108A-S14.108D,S14.109A-S14.109D,S14.111A-S14.111D,S14.112A-S14.112D,S14.113A-S14.113D,S14.114A-S14.114D,S14.115A-S14.115D,S14.116A-S14.116D,S14.117A-S14.117D,S14.118A-S14.118D,S14.119A-S14.119D,S14.121A-S14.121D,S14.122A-S14.122D,S14.123A-S14.123D,S14.124A-S14.124D,S14.125A-S14.125D,S14.126A-S14.126D,S14.127A-S14.127D,S14.128A-S14.128D,S14.129A-S14.129D,S14.131A-S14.131D,S14.132A-S14.132D,S14.133A-S14.133D,S14.134A-S14.134D,S14.135A-S14.135D,S14.136A-S14.136D,S14.137A-S14.137D,S14.138A-S14.138D,S14.139A-S14.139D,S14.141A-S14.141D,S14.142A-S14.142D,S14.143A-S14.143D,S14.144A-S14.144D,S14.145A-S14.145D,S14.146A-S14.146D,S14.147A-S14.147D,S14.148A-S14.148D,S14.149A-S14.149D,S14.151A-S14.151D,S14.152A-S14.152D,S14.153A-S14.153D,S14.154A-S14.154D,S14.155A-S14.155D,S14.156A-S14.156D,S14.157A-S14.157D,S14.158A-S14.158D,S14.159A-S14.159D,S14.2XXA-S14.2XXD,S14.3XXA-S14.3XXD,S24.0XXA-S24.0XXD,S24.101A-S24.101D,S24.102A-S24.102D,S24.103A-S24.103D,S24.104A-S24.104D,S24.109A-S24.109D,S24.111A-S24.111D,S24.112A-S24.112D,S24.113A-S24.113D,S24.114A-S24.114D,S24.119A-S24.119D,S24.131A-S24.131D,S24.132A-S24.132D,S24.133A-S24.133D,S24.134A-S24.134D,S24.139A-S24.139D,S24.141A-S24.141D,S24.142A-S24.142D,S24.143A-S24.143D,S24.144A-S24.144D,S24.149A-S24.149D,S24.151A-S24.151D,S24.152A-S24.152D,S24.153A-S24.153D,S24.154A-S24.154D,S24.159A-S24.159D,S24.2XXA-S24.2XXD,S34.01XA-S34.01XD,S34.02XA-S34.02XD,S34.101A-S34.101D,S34.102A-S34.102D,S34.103A-S34.103D,S34.104A-S34.104D,S34.105A-S34.105D,S34.109A-S34.109D,S34.111A-S34.111D,S34.112A-S34.112D,S34.113A-S34.113D,S34.114A-S34.114D,S34.115A-S34.115D,S34.119A-S34.119D,S34.121A-S34.121D,S34.122A-S34.122D,S34.123A-S34.123D,S34.124A-S34.124D,S34.125A-S34.125D,S34.129A-S34.129D,S34.131A-S34.131D,S34.132A-S34.132D,S34.139A-S34.139D,S34.21XA-S34.21XD,S34.22XA-S34.22XD,S34.3XXA-S34.3XXD,S34.4XXA-S34.4XXD,T40.0X1A-T40.0X1D,T40.0X2A-T40.0X2D,T40.0X3A-T40.0X3D,T40.0X4A-T40.0X4D,T40.1X1A-T40.1X1D,T40.1X2A-T40.1X2D,T40.1X3A-T40.1X3D,T40.1X4A-T40.1X4D,T40.2X1A-T40.2X1D,T40.2X2A-T40.2X2D,T40.2X3A-T40.2X3D,T40.2X4A-T40.2X4D,T40.3X1A-T40.3X1D,T40.3X2A-T40.3X2D,T40.3X3A-T40.3X3D,T40.3X4A-T40.3X4D,T40.4X1A-T40.4X1D,T40.4X2A-T40.4X2D,T40.4X3A-T40.4X3D,T40.4X4A-T40.4X4D,T40.5X1A-T40.5X1D,T40.5X2A-T40.5X2D,T40.5X3A-T40.5X3D,T40.5X4A-T40.5X4D,T40.601A-T40.601D,T40.602A-T40.602D,T40.603A-T40.603D,T40.604A-T40.604D,T40.691A-T40.691D,T40.692A-T40.692D,T40.693A-T40.693D,T40.694A-T40.694D,T40.7X1A-T40.7X1D,T40.7X2A-T40.7X2D,T40.7X3A-T40.7X3D,T40.7X4A-T40.7X4D,T40.8X1A-T40.8X1D,T40.8X2A-T40.8X2D,T40.8X3A-T40.8X3D,T40.8X4A-T40.8X4D,T40.901A-T40.901D,T40.902A-T40.902D,T40.903A-T40.903D,T40.904A-T40.904D,T40.991A-T40.991D,T71.111A-T71.111D,T71.112A-T71.112D,T71.113A-T71.113D,T71.114A-T71.114D,T71.121A-T71.121D,T71.122A-T71.122D,T71.123A-T71.123D,T71.124A-T71.124D,T71.131A-T71.131D,T71.132A-T71.132D,T71.133A-T71.133D,T71.134A-T71.134D,T71.141A-T71.141D,T71.143A-T71.143D,T71.144A-T71.144D,T71.151A-T71.151D,T71.152A-T71.152D,T71.153A-T71.153D,T71.154A-T71.154D,T71.161A-T71.161D,T71.162A-T71.162D,T71.163A-T71.163D,T71.164A-T71.164D,T71.191A-T71.191D,T71.192A-T71.192D,T71.193A-T71.193D,T71.194A-T71.194D,T71.20XA-T71.20XD,T71.21XA-T71.21XD,T71.221A-T71.221D,T71.222A-T71.222D,T71.223A-T71.223D,T71.224A-T71.224D,T71.231A-T71.231D,T71.232A-T71.232D,T71.233A-T71.233D,T71.234A-T71.234D,T71.29XA-T71.29XD,T71.9XXA-T71.9XXD,T74.4XXA-T74.4XXD,T75.01XA-T75.01XD,T75.09XA-T75.09XD,T75.1XXA-T75.1XXD,T75.4XXA-T75.4XXD,T78.00XA-T78.00XD,T78.01XA-T78.01XD,T78.02XA-T78.02XD,T78.03XA-T78.03XD,T78.04XA-T78.04XD,T78.05XA-T78.05XD,T78.06XA-T78.06XD,T78.07XA-T78.07XD,T78.08XA-T78.08XD,T78.09XA-T78.09XD,T78.3XXA-T78.3XXD,T78.8XXA-T78.8XXD,T79.0XXA-T79.0XXD,T79.4XXA-T79.4XXD,T79.6XXA-T79.6XXD,T88.2XXA-T88.2XXD,T88.51XA-T88.51XD,T88.6XXA-T88.6XXD,Z90.02



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CPT: 21084,31611,61215,92507,92508,92521-92524,92607-92609,92633,93792,93793,97012,97110-97127,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513-G0515,S9152

**Line: 346**

Condition: CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS (See Guideline Notes 37,60,64,65,100,101)  
Treatment: SURGICAL THERAPY  
ICD-10: G83.4,M43.10-M43.19,M47.011-M47.27,M48.00-M48.05,M48.061-M48.08,M50.00-M50.01,M50.020-M50.11,M51.04-M51.17,M53.2X1-M53.2X9,M54.10-M54.18,Q06.8,Q76.2  
CPT: 20660-20665,20930-20938,21720,21725,22206-22226,22532-22865,29000-29046,29710,29720,62287,63001-63091,63170,63180-63200,63270-63273,63295-63610,63650,63655,63685,93792,93793,96150-96155,97110-97124,97140-97168,97530,97535,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487,99489,99495,99496,99605-99607  
HCPCS: G0157-G0160,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0508-G0511,G0513,G0514,S2350,S2351

**Line: 347**

Condition: CARDIAC ARRHYTHMIAS (See Guideline Notes 49,64,65,146)  
Treatment: MEDICAL THERAPY, PACEMAKER  
ICD-10: I44.0-I44.2,I44.30-I44.7,I45.0,I45.10-I45.9,I47.1,I47.9,I48.0-I48.4,I48.91-I48.92,I49.1-I49.2,I49.40-I49.9,I97.120-I97.121,R00.1,Z45.010-Z45.09,Z79.01  
CPT: 33202-33229,33233-33238,33250-33261,33265,33266,92960-92971,92978-92998,93279-93284,93286-93289,93292-93296,93600-93642,93650-93657,93724,93745,93792-93798,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0422,G0423,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,K0606-K0609

**Line: 348**

Condition: MILD/MODERATE BIRTH TRAUMA FOR BABY (See Guideline Notes 6,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: P11.1,P11.3-P11.4,P12.0-P12.1,P12.3-P12.4,P12.81-P12.9,P13.0-P13.9,P14.0-P14.9,P15.0-P15.9  
CPT: 22830,67036-67043,67208,67210,67220,67227-67229,67515,92002-92014,92018-92060,92081-92136,92225-92287,93792,93793,96154,96155,97012,97110-97124,97140-97168,97530,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 349**

Condition: NON-LIMB THREATENING PERIPHERAL VASCULAR DISEASE (See Guideline Notes 64,65)  
Treatment: SURGICAL TREATMENT  
ICD-10: E08.51,E09.51,E10.51,E11.51,E13.51,I70.201-I70.209,I70.231-I70.25,I70.291-I70.309,I70.331-I70.35,I70.391-I70.409,I70.431-I70.45,I70.491-I70.509,I70.531-I70.55,I70.591-I70.609,I70.631-I70.65,I70.691-I70.709,I70.731-I70.75,I70.791-I70.92,I74.2-I74.4,I74.9,I75.011-I75.029,I77.1  
CPT: 13160,34101,34111,34201,34203,35081,35256,35286,35302-35321,35351-35372,35500,35510,35512,35516-35525,35533,35539-35558,35565-35587,35606,35621,35623,35646-35661,35665-35671,35682-35686,35700-35761,35860,35875-35881,35903,36002,37184-37186,37211,37213,37214,37220-37235,37246-37249,37609,64802-64818,64821-64823,93668,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 350**

Condition: SARCOIDOSIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: D86.0-D86.3,D86.81-D86.82,D86.84-D86.9  
CPT: 93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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**Line: 351**  
Condition: STRABISMUS DUE TO NEUROLOGIC DISORDER (See Coding Specification Below) (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: H49.00-H49.43,H49.881-H49.9,H51.20-H51.23  
CPT: 15822,15823,65778-65782,66820-66830,66985,66986,67311-67345,67710,67875,67880,67900-67912,67961,67971,68135,68320-68328,68335,68340,68371,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Chemodenervation with botulinum toxin injection (CPT 67345) is included on this line for the treatment of strabismus due to other neurological disorders (ICD-10 H50.89).

**Line: 352**  
Condition: URINARY SYSTEM CALCULUS (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: N20.0-N20.9,N21.0-N21.9,N22  
CPT: 50060-50081,50130,50382-50389,50395,50432-50435,50553,50557,50561,50572,50580,50590,50600,50605,50610-50630,50693-50700,50715,50900,50945,50947,50961-50972,50976,50980,51050-51065,51102,51700,52310-52325,52330-52334,52352,52353,52356,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 353**  
Condition: STRUCTURAL CAUSES OF AMENORRHEA (See Guideline Note 65)  
Treatment: SURGICAL TREATMENT  
ICD-10: N85.7,N89.5-N89.7,N92.5,N93.8,N99.2,Q51.0,Q51.5,Q51.7,Q51.820-Q51.9,Q52.0,Q52.10-Q52.11,Q52.121-Q52.8,Z43.7  
CPT: 56441,56442,56700,56800,57130,57291-57295,57400,57426,57800,58120,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 354**  
Condition: PENETRATING WOUND OF ORBIT (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: H05.50-H05.53,S01.101A-S01.101D,S01.102A-S01.102D,S01.109A-S01.109D,S05.40XA-S05.40XD,S05.41XA-S05.41XD,S05.42XA-S05.42XD  
CPT: 12011,12013,12051,12052,13132,13151,13152,67405-67414,67420-67445,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 355**  
Condition: CLOSED FRACTURE OF EXTREMITIES (EXCEPT MINOR TOES) (See Guideline Notes 6,64,65)  
Treatment: OPEN OR CLOSED REDUCTION  
ICD-10: M24.029,M80.00XA,M80.011A-M80.011G,M80.012A-M80.012G,M80.019A-M80.019G,M80.021A-M80.021G,M80.022A-M80.022G,M80.029A-M80.029G,M80.031A-M80.031G,M80.032A-M80.032G,M80.039A-M80.039G,M80.041A-M80.041G,M80.042A-M80.042G,M80.049A-M80.049G,M80.051A-M80.051G,M80.052A-M80.052G,M80.059A-M80.059G,M80.061A-M80.061G,M80.062A-M80.062G,M80.069A-M80.069G,M80.071A-M80.071G,M80.072A-M80.072G,M80.079A-M80.079G,M80.80XA,M80.811A-M80.811G,M80.812A-M80.812G,M80.819A-M80.819G,M80.821A-M80.821G,M80.822A-M80.822G,M80.829A-M80.829G,M80.831A-M80.831G,M80.832A-M80.832G,M80.839A-M80.839G,M80.841A-M80.841G,M80.842A-M80.842G,M80.849A-M80.849G,M80.851A-M80.851G,M80.852A-M80.852G,M80.859A-M80.859G,M80.861A-M80.861G,M80.862A-M80.862G,M80.869A-M80.869G,M80.871A-M80.871G,M80.872A-M80.872G,M80.879A-M80.879G,M84.30XA,M84.311A-M84.311G,M84.312A-M84.312G,M84.319A-M84.319G,M84.321A-M84.321G,M84.322A-M84.322G,M84.329A-M84.329G,M84.331A-M84.331G,M84.332A-M84.332G,M84.333A-M84.333G,M84.334A-M84.334G,M84.339A-M84.339G,M84.341A-M84.341G,M84.342A-M84.342G,M84.343A-M84.343G,M84.344A-M84.344G,M84.345A-M84.345G,M84.346A-M84.346G,M84.351A-M84.351G,M84.352A-M84.352G,M84.353A-M84.353G,M84.361A-M84.361G,M84.362A-M84.362G,M84.363A-M84.363G,M84.364A-M84.364G,M84.369A-M84.369G,M84.371A-M84.371G,M84.372A-M84.372G,M84.373A-M84.373G,M84.374A-M84.374G,M84.375A-M84.375G,M84.376A-M84.376G,M84.38XA,M84.40XA,M84.411A-M84.411G,M84.412A-M84.412G,M84.419A-M84.419G,M84.421A-M84.421G,M84.422A-M84.422G,M84.429A-M84.429G,M84.431A-M84.431G,M84.432A-M84.432G,M84.433A-M84.433G,M84.434A-M84.434G,M84.439A-M84.439G,M84.441A-M84.441G,M84.442A-M84.442G,M84.443A-M84.443G,M84.444A-M84.444G,M84.445A-M84.445G,M84.446A-M84.446G,M84.451A-M84.451G,M84.452A-M84.452G,M84.453A-M84.453G,M84.461A-M84.461G,M84.462A-M84.462G,M84.463A-M84.463G,M84.464A-M84.464G,M84.469A-M84.469G,M84.471A-M84.471G,M84.472A-M84.472G,M84.473A-M84.473G,M84.474A-M84.474G,M84.475A-M84.475G,M84.476A-M84.476G,M84.48XA,M84.50XA,M84.511A-M84.511G,M84.512A-M84.512G,



PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

M84.519A-M84.519G,M84.521A-M84.521G,M84.522A-M84.522G,M84.529A-M84.529G,M84.531A-M84.531G,  
M84.532A-M84.532G,M84.533A-M84.533G,M84.534A-M84.534G,M84.539A-M84.539G,M84.541A-M84.541G,  
M84.542A-M84.542G,M84.549A-M84.549G,M84.551A-M84.551G,M84.552A-M84.552G,M84.553A-M84.553G,  
M84.561A-M84.561G,M84.562A-M84.562G,M84.563A-M84.563G,M84.564A-M84.564G,M84.569A-M84.569G,  
M84.571A-M84.571G,M84.572A-M84.572G,M84.573A-M84.573G,M84.574A-M84.574G,M84.575A-M84.575G,  
M84.576A-M84.576G,M84.58XD-M84.58XG,M84.60XA,M84.611A-M84.611G,M84.612A-M84.612G,M84.619A-  
M84.619G,M84.621A-M84.621G,M84.622A-M84.622G,M84.629A-M84.629G,M84.631A-M84.631G,M84.632A-  
M84.632G,M84.633A-M84.633G,M84.634A-M84.634G,M84.639A-M84.639G,M84.641A-M84.641G,M84.642A-  
M84.642G,M84.649A-M84.649G,M84.651A-M84.651G,M84.652A-M84.652G,M84.653A-M84.653G,M84.661A-  
M84.661G,M84.662A-M84.662G,M84.663A-M84.663G,M84.664A-M84.664G,M84.669A-M84.669G,M84.671A-  
M84.671G,M84.672A-M84.672G,M84.673A-M84.673G,M84.674A-M84.674G,M84.675A-M84.675G,M84.676A-  
M84.676G,M84.750A-M84.750G,M84.751A-M84.751G,M84.752A-M84.752G,M84.753A-M84.753G,M84.754A-  
M84.754G,M84.755A-M84.755G,M84.756A-M84.756G,M84.757A-M84.757G,M84.758A-M84.758G,M84.759A-  
M84.759G,M93.001-M93.033,S32.446D,S42.001A,S42.001D-S42.001G,S42.002A,S42.002D-S42.002G,  
S42.009A,S42.009D-S42.009G,S42.011A,S42.011D-S42.011G,S42.012A,S42.012D-S42.012G,S42.013A,  
S42.013D-S42.013G,S42.014A,S42.014D-S42.014G,S42.015A,S42.015D-S42.015G,S42.016A,S42.016D-  
S42.016G,S42.017A,S42.017D-S42.017G,S42.018A,S42.018D-S42.018G,S42.019A,S42.019D-S42.019G,  
S42.021A,S42.021D-S42.021G,S42.022A,S42.022D-S42.022G,S42.023A,S42.023D-S42.023G,S42.024A,  
S42.024D-S42.024G,S42.025A,S42.025D-S42.025G,S42.026A,S42.026D-S42.026G,S42.031A,S42.031D-  
S42.031G,S42.032A,S42.032D-S42.032G,S42.033A,S42.033D-S42.033G,S42.034A,S42.034D-S42.034G,  
S42.035A,S42.035D-S42.035G,S42.036A,S42.036D-S42.036G,S42.101A,S42.101D-S42.101G,S42.102A,  
S42.102D-S42.102G,S42.109A,S42.109D-S42.109G,S42.111A,S42.111D-S42.111G,S42.112A,S42.112D-  
S42.112G,S42.113A,S42.113D-S42.113G,S42.114A,S42.114D-S42.114G,S42.115A,S42.115D-S42.115G,  
S42.116A,S42.116D-S42.116G,S42.121A,S42.121D-S42.121G,S42.122A,S42.122D-S42.122G,S42.123A,  
S42.123D-S42.123G,S42.124A,S42.124D-S42.124G,S42.125A,S42.125D-S42.125G,S42.126A,S42.126D-  
S42.126G,S42.131A,S42.131D-S42.131G,S42.132A,S42.132D-S42.132G,S42.133A,S42.133D-S42.133G,  
S42.134A,S42.134D-S42.134G,S42.135A,S42.135D-S42.135G,S42.136A,S42.136D-S42.136G,S42.141A,  
S42.141D-S42.141G,S42.142A,S42.142D-S42.142G,S42.143A,S42.143D-S42.143G,S42.144A,S42.144D-  
S42.144G,S42.145A,S42.145D-S42.145G,S42.146A,S42.146D-S42.146G,S42.151A,S42.151D-S42.151G,  
S42.152A,S42.152D-S42.152G,S42.153A,S42.153D-S42.153G,S42.154A,S42.154D-S42.154G,S42.155A,  
S42.155D-S42.155G,S42.156A,S42.156D-S42.156G,S42.191A,S42.191D-S42.191G,S42.192A,S42.192D-  
S42.192G,S42.199A,S42.199D-S42.199G,S42.201A,S42.201D-S42.201G,S42.202A,S42.202D-S42.202G,  
S42.209A,S42.209D-S42.209G,S42.211A,S42.211D-S42.211G,S42.212A,S42.212D-S42.212G,S42.213A,  
S42.213D-S42.213G,S42.214A,S42.214D-S42.214G,S42.215A,S42.215D-S42.215G,S42.216A,S42.216D-  
S42.216G,S42.221A,S42.221D-S42.221G,S42.222A,S42.222D-S42.222G,S42.223A,S42.223D-S42.223G,  
S42.224A,S42.224D-S42.224G,S42.225A,S42.225D-S42.225G,S42.226A,S42.226D-S42.226G,S42.231A,  
S42.231D-S42.231G,S42.232A,S42.232D-S42.232G,S42.239A,S42.239D-S42.239G,S42.241A,S42.241D-  
S42.241G,S42.242A,S42.242D-S42.242G,S42.249A,S42.249D-S42.249G,S42.251A,S42.251D-S42.251G,  
S42.252A,S42.252D-S42.252G,S42.253A,S42.253D-S42.253G,S42.254A,S42.254D-S42.254G,S42.255A,  
S42.255D-S42.255G,S42.256A,S42.256D-S42.256G,S42.261A,S42.261D-S42.261G,S42.262A,S42.262D-  
S42.262G,S42.263A,S42.263D-S42.263G,S42.264A,S42.264D-S42.264G,S42.265A,S42.265D-S42.265G,  
S42.266A,S42.266D-S42.266G,S42.271A-S42.271G,S42.272A-S42.272G,S42.279A-S42.279G,S42.291A,  
S42.291D-S42.291G,S42.292A,S42.292D-S42.292G,S42.293A,S42.293D-S42.293G,S42.294A,S42.294D-  
S42.294G,S42.295A,S42.295D-S42.295G,S42.296A,S42.296D-S42.296G,S42.301A,S42.301D-S42.301G,  
S42.302A,S42.302D-S42.302G,S42.309A,S42.309D-S42.309G,S42.311A-S42.311G,S42.312A-S42.312G,  
S42.319A-S42.319G,S42.321A,S42.321D-S42.321G,S42.322A,S42.322D-S42.322G,S42.323A,S42.323D-  
S42.323G,S42.324A,S42.324D-S42.324G,S42.325A,S42.325D-S42.325G,S42.326A,S42.326D-S42.326G,  
S42.331A,S42.331D-S42.331G,S42.332A,S42.332D-S42.332G,S42.333A,S42.333D-S42.333G,S42.334A,  
S42.334D-S42.334G,S42.335A,S42.335D-S42.335G,S42.336A,S42.336D-S42.336G,S42.341A,S42.341D-  
S42.341G,S42.342A,S42.342D-S42.342G,S42.343A,S42.343D-S42.343G,S42.344A,S42.344D-S42.344G,  
S42.345A,S42.345D-S42.345G,S42.346A,S42.346D-S42.346G,S42.351A,S42.351D-S42.351G,S42.352A,  
S42.352D-S42.352G,S42.353A,S42.353D-S42.353G,S42.354A,S42.354D-S42.354G,S42.355A,S42.355D-  
S42.355G,S42.356A,S42.356D-S42.356G,S42.361A,S42.361D-S42.361G,S42.362A,S42.362D-S42.362G,  
S42.363A,S42.363D-S42.363G,S42.364A,S42.364D-S42.364G,S42.365A,S42.365D-S42.365G,S42.366A,  
S42.366D-S42.366G,S42.391A,S42.391D-S42.391G,S42.392A,S42.392D-S42.392G,S42.399A,S42.399D-  
S42.399G,S42.401A,S42.401D-S42.401G,S42.402A,S42.402D-S42.402G,S42.409A,S42.409D-S42.409G,  
S42.411A,S42.411D-S42.411G,S42.412A,S42.412D-S42.412G,S42.413A,S42.413D-S42.413G,S42.414A,  
S42.414D-S42.414G,S42.415A,S42.415D-S42.415G,S42.416A,S42.416D-S42.416G,S42.421A,S42.421D-  
S42.421G,S42.422A,S42.422D-S42.422G,S42.423A,S42.423D-S42.423G,S42.424A,S42.424D-S42.424G,  
S42.425A,S42.425D-S42.425G,S42.426A,S42.426D-S42.426G,S42.431A,S42.431D-S42.431G,S42.432A,  
S42.432D-S42.432G,S42.433A,S42.433D-S42.433G,S42.434A,S42.434D-S42.434G,S42.435A,S42.435D-  
S42.435G,S42.436A,S42.436D-S42.436G,S42.441A,S42.441D-S42.441G,S42.442A,S42.442D-S42.442G,  
S42.443A,S42.443D-S42.443G,S42.444A,S42.444D-S42.444G,S42.445A,S42.445D-S42.445G,S42.446A,  
S42.446D-S42.446G,S42.447A,S42.447D-S42.447G,S42.448A,S42.448D-S42.448G,S42.449A,S42.449D-  
S42.449G,S42.451A,S42.451D-S42.451G,S42.452A,S42.452D-S42.452G,S42.453A,S42.453D-S42.453G,  
S42.454A,S42.454D-S42.454G,S42.455A,S42.455D-S42.455G,S42.456A,S42.456D-S42.456G,S42.461A,  
S42.461D-S42.461G,S42.462A,S42.462D-S42.462G,S42.463A,S42.463D-S42.463G,S42.464A,S42.464D-  
S42.464G,S42.465A,S42.465D-S42.465G,S42.466A,S42.466D-S42.466G,S42.471A,S42.471D-S42.471G,  
S42.472A,S42.472D-S42.472G,S42.473A,S42.473D-S42.473G,S42.474A,S42.474D-S42.474G,S42.475A,  
S42.475D-S42.475G,S42.476A,S42.476D-S42.476G,S42.481A-S42.481G,S42.482A-S42.482G,S42.489A-  
S42.489G,S42.491A,S42.491D-S42.491G,S42.492A,S42.492D-S42.492G,S42.493A,S42.493D-S42.493G,  
S42.494A,S42.494D-S42.494G,S42.495A,S42.495D-S42.495G,S42.496A,S42.496D-S42.496G,S42.90XA,



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JANUARY 1, 2018 (REVISED)

S42.90XD-S42.90XG,S42.91XA,S42.91XD-S42.91XG,S42.92XA,S42.92XD-S42.92XG,S49.001A-S49.001G,  
S49.002A-S49.002G,S49.009A-S49.009G,S49.011A-S49.011G,S49.012A-S49.012G,S49.019A-S49.019G,  
S49.021A-S49.021G,S49.022A-S49.022G,S49.029A-S49.029G,S49.031A-S49.031G,S49.032A-S49.032G,  
S49.039A-S49.039G,S49.041A-S49.041G,S49.042A-S49.042G,S49.049A-S49.049G,S49.091A-S49.091G,  
S49.092A-S49.092G,S49.099A-S49.099G,S49.101A-S49.101G,S49.102A-S49.102G,S49.109A-S49.109G,  
S49.111A-S49.111G,S49.112A-S49.112G,S49.119A-S49.119G,S49.121A-S49.121G,S49.122A-S49.122G,  
S49.129A-S49.129G,S49.131A-S49.131G,S49.132A-S49.132G,S49.139A-S49.139G,S49.141A-S49.141G,  
S49.142A-S49.142G,S49.149A-S49.149G,S49.191A-S49.191G,S49.192A-S49.192G,S49.199A-S49.199G,  
S52.001A,S52.001D,S52.001G,S52.002A,S52.002D,S52.002G,S52.002J,S52.009A,S52.009D,S52.009G,  
S52.011A-S52.011G,S52.012A-S52.012G,S52.019A-S52.019G,S52.021A,S52.021D,S52.021G,S52.022A,  
S52.022D,S52.022G,S52.023A,S52.023D,S52.023G,S52.024A,S52.024D,S52.024G,S52.025A,S52.025D,  
S52.025G,S52.026A,S52.026D,S52.026G,S52.031A,S52.031D,S52.031G,S52.032A,S52.032D,S52.032G,  
S52.033A,S52.033D,S52.033G,S52.034A,S52.034D,S52.034G,S52.035A,S52.035D,S52.035G,S52.036A,  
S52.036D,S52.036G,S52.041A,S52.041D,S52.041G,S52.042A,S52.042D,S52.042G,S52.043A,S52.043D,  
S52.043G,S52.044A,S52.044D,S52.044G,S52.045A,S52.045D,S52.045G,S52.046A,S52.046D,S52.046G,  
S52.091A,S52.091D,S52.091G,S52.092A,S52.092D,S52.092G,S52.099A,S52.099D,S52.099G,S52.101A,  
S52.101D,S52.101G,S52.102A,S52.102D,S52.102G,S52.109A,S52.109D,S52.109G,S52.111A-S52.111G,  
S52.112A-S52.112G,S52.119A-S52.119G,S52.121A,S52.121D,S52.121G,S52.122A,S52.122D,S52.122G,  
S52.123A,S52.123D,S52.123G,S52.124A,S52.124D,S52.124G,S52.125A,S52.125D,S52.125G,S52.126A,  
S52.126D,S52.126G,S52.131A,S52.131D,S52.131G,S52.132A,S52.132D,S52.132G,S52.133A,S52.133D,  
S52.133G,S52.134A,S52.134D,S52.134G,S52.135A,S52.135D,S52.135G,S52.136A,S52.136D,S52.136G,  
S52.181A,S52.181D,S52.181G,S52.182A,S52.182D,S52.182G,S52.189A,S52.189D,S52.189G,S52.201A,  
S52.201D,S52.201G,S52.202A,S52.202D,S52.202G,S52.209A,S52.209D,S52.209G,S52.211A-S52.211G,  
S52.212A-S52.212G,S52.219A-S52.219G,S52.221A,S52.221D,S52.221G,S52.222A,S52.222D,S52.222G,  
S52.223A,S52.223D,S52.223G,S52.224A,S52.224D,S52.224G,S52.225A,S52.225D,S52.225G,S52.226A,  
S52.226D,S52.226G,S52.231A,S52.231D,S52.231G,S52.232A,S52.232D,S52.232G,S52.233A,S52.233D,  
S52.233G,S52.234A,S52.234D,S52.234G,S52.235A,S52.235D,S52.235G,S52.236A,S52.236D,S52.236G,  
S52.241A,S52.241D,S52.241G,S52.242A,S52.242D,S52.242G,S52.243A,S52.243D,S52.243G,S52.244A,  
S52.244D,S52.244G,S52.245A,S52.245D,S52.245G,S52.246A,S52.246D,S52.246G,S52.251A,S52.251D,  
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S59.121A-S59.121G,S59.122A-S59.122G,S59.129A-S59.129G,S59.131A-S59.131G,S59.132A-S59.132G,  
S59.139A-S59.139G,S59.141A-S59.141G,S59.142A-S59.142G,S59.149A-S59.149G,S59.191A-S59.191G,  
S59.192A-S59.192G,S59.199A-S59.199G,S59.201A-S59.201G,S59.202A-S59.202G,S59.209A-S59.209G,  
S59.211A-S59.211G,S59.212A-S59.212G,S59.219A-S59.219G,S59.221A-S59.221G,S59.222A-S59.222G,  
S59.229A-S59.229G,S59.231A-S59.231G,S59.232A-S59.232G,S59.239A-S59.239G,S59.241A-S59.241G,



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S59.242A-S59.242G,S59.249A-S59.249G,S59.291A-S59.291G,S59.292A-S59.292G,S59.299A-S59.299G,  
S62.001A,S62.001D-S62.001G,S62.002A,S62.002D-S62.002G,S62.009A,S62.009D-S62.009G,S62.011A,  
S62.011D-S62.011G,S62.012A,S62.012D-S62.012G,S62.013A,S62.013D-S62.013G,S62.014A,S62.014D-  
S62.014G,S62.015A,S62.015D-S62.015G,S62.016A,S62.016D-S62.016G,S62.021A,S62.021D-S62.021G,  
S62.022A,S62.022D-S62.022G,S62.023A,S62.023D-S62.023G,S62.024A,S62.024D-S62.024G,S62.025A,  
S62.025D-S62.025G,S62.026A,S62.026D-S62.026G,S62.031A,S62.031D-S62.031G,S62.032A,S62.032D-  
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S62.036A,S62.036D-S62.036G,S62.101A,S62.101D-S62.101G,S62.102A,S62.102D-S62.102G,S62.109A,  
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S62.171A,S62.171D-S62.171G,S62.172A,S62.172D-S62.172G,S62.173A,S62.173D-S62.173G,S62.174A,  
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S62.202D-S62.202G,S62.209A,S62.209D-S62.209G,S62.211A,S62.211D-S62.211G,S62.212A,S62.212D-  
S62.212G,S62.213A,S62.213D-S62.213G,S62.221A,S62.221D-S62.221G,S62.222A,S62.222D-S62.222G,  
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S62.613D-S62.613G,S62.614A,S62.614D-S62.614G,S62.615A,S62.615D-S62.615G,S62.616A,S62.616D-  
S62.616G,S62.617A,S62.617D-S62.617G,S62.618A,S62.618D-S62.618G,S62.619A,S62.619D-S62.619G,  
S62.620A,S62.620D-S62.620G,S62.621A,S62.621D-S62.621G,S62.622A,S62.622D-S62.622G,S62.623A,  
S62.623D-S62.623G,S62.624A,S62.624D-S62.624G,S62.625A,S62.625D-S62.625G,S62.626A,S62.626D-  
S62.626G,S62.627A,S62.627D-S62.627G,S62.628A,S62.628D-S62.628G,S62.629A,S62.629D-S62.629G,  
S62.630A,S62.630D-S62.630G,S62.631A,S62.631D-S62.631G,S62.632A,S62.632D-S62.632G,S62.633A,  
S62.633D-S62.633G,S62.634A,S62.634D-S62.634G,S62.635A,S62.635D-S62.635G,S62.636A,S62.636D-



PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

S62.636G,S62.637A,S62.637D-S62.637G,S62.638A,S62.638D-S62.638G,S62.639A,S62.639D-S62.639G,  
S62.640A,S62.640D-S62.640G,S62.641A,S62.641D-S62.641G,S62.642A,S62.642D-S62.642G,S62.643A,  
S62.643D-S62.643G,S62.644A,S62.644D-S62.644G,S62.645A,S62.645D-S62.645G,S62.646A,S62.646D-  
S62.646G,S62.647A,S62.647D-S62.647G,S62.648A,S62.648D-S62.648G,S62.649A,S62.649D-S62.649G,  
S62.650A,S62.650D-S62.650G,S62.651A,S62.651D-S62.651G,S62.652A,S62.652D-S62.652G,S62.653A,  
S62.653D-S62.653G,S62.654A,S62.654D-S62.654G,S62.655A,S62.655D-S62.655G,S62.656A,S62.656D-  
S62.656G,S62.657A,S62.657D-S62.657G,S62.658A,S62.658D-S62.658G,S62.659A,S62.659D-S62.659G,  
S62.660A,S62.660D-S62.660G,S62.661A,S62.661D-S62.661G,S62.662A,S62.662D-S62.662G,S62.663A,  
S62.663D-S62.663G,S62.664A,S62.664D-S62.664G,S62.665A,S62.665D-S62.665G,S62.666A,S62.666D-  
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PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

S82.302D,S82.302G,S82.309A,S82.309D,S82.309G,S82.311A-S82.311G,S82.312A-S82.312G,S82.319A-S82.319G,S82.391A,S82.391D,S82.391G,S82.392A,S82.392D,S82.392G,S82.399A,S82.399D,S82.399G,S82.401A,S82.401D,S82.401G,S82.402A,S82.402D,S82.402G,S82.409A,S82.409D,S82.409G,S82.421A,S82.421D,S82.421G,S82.422A,S82.422D,S82.422G,S82.423A,S82.423D,S82.423G,S82.424A,S82.424D,S82.424G,S82.425A,S82.425D,S82.425G,S82.426A,S82.426D,S82.426G,S82.431A,S82.431D,S82.431G,S82.432A,S82.432D,S82.432G,S82.433A,S82.433D,S82.433G,S82.434A,S82.434D,S82.434G,S82.435A,S82.435D,S82.435G,S82.436A,S82.436D,S82.436G,S82.441A,S82.441D,S82.441G,S82.442A,S82.442D,S82.442G,S82.442J,S82.443A,S82.443D,S82.443G,S82.444A,S82.444D,S82.444G,S82.445A,S82.445D,S82.445G,S82.446A,S82.446D,S82.446G,S82.451A,S82.451D,S82.451G,S82.452A,S82.452D,S82.452G,S82.453A,S82.453D,S82.453G,S82.454A,S82.454D,S82.454G,S82.455A,S82.455D,S82.455G,S82.456A,S82.456D,S82.456G,S82.461A,S82.461D,S82.461G,S82.462A,S82.462D,S82.462G,S82.463A,S82.463D,S82.463G,S82.464A,S82.464D,S82.464G,S82.465A,S82.465D,S82.465G,S82.466A,S82.466D,S82.466G,S82.491A,S82.491D,S82.491G,S82.492A,S82.492D,S82.492G,S82.499A,S82.499D,S82.499G,S82.51XA,S82.51XD,S82.51XG,S82.52XA,S82.52XD,S82.52XG,S82.53XA,S82.53XD,S82.53XG,S82.54XA,S82.54XD,S82.54XG,S82.55XA,S82.55XD,S82.55XG,S82.56XA,S82.56XD,S82.56XG,S82.61XA,S82.61XD,S82.61XG,S82.62XA,S82.62XD,S82.62XG,S82.63XA,S82.63XD,S82.63XG,S82.64XA,S82.64XD,S82.64XG,S82.65XA,S82.65XD,S82.65XG-S82.65XJ,S82.66XA,S82.66XD,S82.66XG,S82.811A-S82.811G,S82.812A-S82.812G,S82.819A-S82.819G,S82.821A-S82.821G,S82.822A-S82.822G,S82.829A-S82.829G,S82.831A,S82.831D,S82.831G,S82.832A,S82.832D,S82.832G,S82.839A,S82.839D,S82.839G,S82.841A,S82.841D,S82.841G,S82.842A,S82.842D,S82.842G,S82.843A,S82.843D,S82.843G,S82.844A,S82.844D,S82.844G,S82.845A,S82.845D,S82.845G,S82.846A,S82.846D,S82.846G,S82.851A,S82.851D,S82.851G,S82.852A,S82.852D,S82.852G,S82.853A,S82.853D,S82.853G,S82.854A,S82.854D,S82.854G,S82.855A,S82.855D,S82.855G,S82.856A,S82.856D,S82.856G,S82.861A,S82.861D,S82.861G,S82.862A,S82.862D,S82.862G,S82.863A,S82.863D,S82.863G,S82.864A,S82.864D,S82.864G,S82.865A,S82.865D,S82.865G,S82.866A,S82.866D,S82.866G,S82.871A,S82.871D,S82.871G,S82.872A,S82.872D,S82.872G,S82.873A,S82.873D,S82.873G,S82.874A,S82.874D,S82.874G,S82.875A,S82.875D,S82.875G,S82.876A,S82.876D,S82.876G,S82.891A,S82.891D,S82.891G,S82.892A,S82.892D,S82.892G,S82.899A,S82.899D,S82.899G,S82.90XA,S82.90XD,S82.90XG,S82.91XA,S82.91XD,S82.91XG,S82.92XA,S82.92XD,S82.92XG,S89.001A-S89.001G,S89.002A-S89.002G,S89.009A-S89.009G,S89.011A-S89.011G,S89.012A-S89.012G,S89.019A-S89.019G,S89.021A-S89.021G,S89.022A-S89.022G,S89.029A-S89.029G,S89.031A-S89.031G,S89.032A-S89.032G,S89.039A-S89.039G,S89.041A-S89.041G,S89.042A-S89.042G,S89.049A-S89.049G,S89.091A-S89.091G,S89.092A-S89.092G,S89.099A-S89.099G,S89.101A-S89.101G,S89.102A-S89.102G,S89.109A-S89.109G,S89.111A-S89.111G,S89.112A-S89.112G,S89.119A-S89.119G,S89.121A-S89.121G,S89.122A-S89.122G,S89.129A-S89.129G,S89.131A-S89.131G,S89.132A-S89.132G,S89.139A-S89.139G,S89.141A-S89.141G,S89.142A-S89.142G,S89.149A-S89.149G,S89.191A-S89.191G,S89.192A-S89.192G,S89.199A-S89.199G,S89.201A-S89.201G,S89.202A-S89.202G,S89.209A-S89.209G,S89.211A-S89.211G,S89.212A-S89.212G,S89.219A-S89.219G,S89.221A-S89.221G,S89.222A-S89.222G,S89.229A-S89.229G,S89.291A-S89.291G,S89.292A-S89.292G,S89.299A-S89.299G,S89.301A-S89.301G,S89.302A-S89.302G,S89.309A-S89.309G,S89.311A-S89.311G,S89.312A-S89.312G,S89.319A-S89.319G,S89.321A-S89.321G,S89.322A-S89.322G,S89.329A-S89.329G,S89.391A-S89.391G,S89.392A-S89.392G,S89.399A-S89.399G,S92.001A,S92.001D-S92.001G,S92.002A,S92.002D-S92.002G,S92.009A,S92.009D-S92.009G,S92.011A,S92.011D-S92.011G,S92.012A,S92.012D-S92.012G,S92.013A,S92.013D-S92.013G,S92.014A,S92.014D-S92.014G,S92.015A,S92.015D-S92.015G,S92.016A,S92.016D-S92.016G,S92.021A,S92.021D-S92.021G,S92.022A,S92.022D-S92.022G,S92.023A,S92.023D-S92.023G,S92.024A,S92.024D-S92.024G,S92.025A,S92.025D-S92.025G,S92.026A,S92.026D-S92.026G,S92.031A,S92.031D-S92.031G,S92.032A,S92.032D-S92.032G,S92.033A,S92.033D-S92.033G,S92.034A,S92.034D-S92.034G,S92.035A,S92.035D-S92.035G,S92.036A,S92.036D-S92.036G,S92.041A,S92.041D-S92.041G,S92.042A,S92.042D-S92.042G,S92.043A,S92.043D-S92.043G,S92.044A,S92.044D-S92.044G,S92.045A,S92.045D-S92.045G,S92.046A,S92.046D-S92.046G,S92.051A,S92.051D-S92.051G,S92.052A,S92.052D-S92.052G,S92.053A,S92.053D-S92.053G,S92.054A,S92.054D-S92.054G,S92.055A,S92.055D-S92.055G,S92.056A,S92.056D-S92.056G,S92.061A,S92.061D-S92.061G,S92.062A,S92.062D-S92.062G,S92.063A,S92.063D-S92.063G,S92.064A,S92.064D-S92.064G,S92.065A,S92.065D-S92.065G,S92.066A,S92.066D-S92.066G,S92.101A,S92.101D-S92.101G,S92.102A,S92.102D-S92.102G,S92.109A,S92.109D-S92.109G,S92.111A,S92.111D-S92.111G,S92.112A,S92.112D-S92.112G,S92.113A,S92.113D-S92.113G,S92.114A,S92.114D-S92.114G,S92.115A,S92.115D-S92.115G,S92.116A,S92.116D-S92.116G,S92.121A,S92.121D-S92.121G,S92.122A,S92.122D-S92.122G,S92.123A,S92.123D-S92.123G,S92.124A,S92.124D-S92.124G,S92.125A,S92.125D-S92.125G,S92.126A,S92.126D-S92.126G,S92.131A,S92.131D-S92.131G,S92.132A,S92.132D-S92.132G,S92.133A,S92.133D-S92.133G,S92.134A,S92.134D-S92.134G,S92.135A,S92.135D-S92.135G,S92.136A,S92.136D-S92.136G,S92.141A,S92.141D-S92.141G,S92.142A,S92.142D-S92.142G,S92.143A,S92.143D-S92.143G,S92.144A,S92.144D-S92.144G,S92.145A,S92.145D-S92.145G,S92.146A,S92.146D-S92.146G,S92.151A,S92.151D-S92.151G,S92.152A,S92.152D-S92.152G,S92.153A,S92.153D-S92.153G,S92.154A,S92.154D-S92.154G,S92.155A,S92.155D-S92.155G,S92.156A,S92.156D-S92.156G,S92.191A,S92.191D-S92.191G,S92.192A,S92.192D-S92.192G,S92.199A,S92.199D-S92.199G,S92.201A,S92.201D-S92.201G,S92.202A,S92.202D-S92.202G,S92.209A,S92.209D-S92.209G,S92.211A,S92.211D-S92.211G,S92.212A,S92.212D-S92.212G,S92.213A,S92.213D-S92.213G,S92.214A,S92.214D-S92.214G,S92.215A,S92.215D-S92.215G,S92.216A,S92.216D-S92.216G,S92.221A,S92.221D-S92.221G,S92.222A,S92.222D-S92.222G,S92.223A,S92.223D-S92.223G,S92.224A,S92.224D-S92.224G,S92.225A,S92.225D-S92.225G,S92.226A,S92.226D-S92.226G,S92.231A,S92.231D-S92.231G,S92.232A,S92.232D-S92.232G,S92.233A,S92.233D-S92.233G,S92.234A,S92.234D-S92.234G,S92.235A,S92.235D-S92.235G,S92.236A,S92.236D-S92.236G,S92.241A,S92.241D-S92.241G,S92.242A,S92.242D-S92.242G,S92.243A,S92.243D-S92.243G,S92.244A,S92.244D-S92.244G,S92.245A,S92.245D-S92.245G,S92.246A,S92.246D-S92.246G,S92.251A,S92.251D-S92.251G,S92.252A,S92.252D-S92.252G,S92.253A,S92.253D-S92.253G,S92.254A,S92.254D-S92.254G,S92.255A,S92.255D-S92.255G,S92.256A,S92.256D-S92.256G



PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

S92.256G,S92.301A,S92.301D-S92.301G,S92.302A,S92.302D-S92.302G,S92.309A,S92.309D-S92.309G,  
S92.311A,S92.311D-S92.311G,S92.312A,S92.312D-S92.312G,S92.313A,S92.313D-S92.313G,S92.314A,  
S92.314D-S92.314G,S92.315A,S92.315D-S92.315G,S92.316A,S92.316D-S92.316G,S92.321A,S92.321D-  
S92.321G,S92.322A,S92.322D-S92.322G,S92.323A,S92.323D-S92.323G,S92.324A,S92.324D-S92.324G,  
S92.325A,S92.325D-S92.325G,S92.326A,S92.326D-S92.326G,S92.331A,S92.331D-S92.331G,S92.332A,  
S92.332D-S92.332G,S92.333A,S92.333D-S92.333G,S92.334A,S92.334D-S92.334G,S92.335A,S92.335D-  
S92.335G,S92.336A,S92.336D-S92.336G,S92.341A,S92.341D-S92.341G,S92.342A,S92.342D-S92.342G,  
S92.343A,S92.343D-S92.343G,S92.344A,S92.344D-S92.344G,S92.345A,S92.345D-S92.345G,S92.346A,  
S92.346D-S92.346G,S92.351A,S92.351D-S92.351G,S92.352A,S92.352D-S92.352G,S92.353A,S92.353D-  
S92.353G,S92.354A,S92.354D-S92.354G,S92.355A,S92.355D-S92.355G,S92.356A,S92.356D-S92.356G,  
S92.401A,S92.401D-S92.401G,S92.402A,S92.402D-S92.402G,S92.403A,S92.403D-S92.403G,S92.404A,  
S92.404D-S92.404G,S92.405A,S92.405D-S92.405G,S92.406A,S92.406D-S92.406G,S92.411A,S92.411D-  
S92.411G,S92.412A,S92.412D-S92.412G,S92.413A,S92.413D-S92.413G,S92.414A,S92.414D-S92.414G,  
S92.415A,S92.415D-S92.415G,S92.416A,S92.416D-S92.416G,S92.421A,S92.421D-S92.421G,S92.422A,  
S92.422D-S92.422G,S92.423A,S92.423D-S92.423G,S92.424A,S92.424D-S92.424G,S92.425A,S92.425D-  
S92.425G,S92.426A,S92.426D-S92.426G,S92.491A,S92.491D-S92.491G,S92.492A,S92.492D-S92.492G,  
S92.499A,S92.499D-S92.499G,S92.811A,S92.811D-S92.811G,S92.812A,S92.812D-S92.812G,S92.819A,  
S92.819D-S92.819G,S92.901A,S92.901D,S92.902A,S92.902D,S92.909A,S92.909D,S99.001A,S99.001D-  
S99.001G,S99.002A,S99.002D-S99.002G,S99.009A,S99.009D-S99.009G,S99.011A,S99.011D-S99.011G,  
S99.012A,S99.012D-S99.012G,S99.019A,S99.019D-S99.019G,S99.021A,S99.021D-S99.021G,S99.022A,  
S99.022D-S99.022G,S99.029A,S99.029D-S99.029G,S99.031A,S99.031D-S99.031G,S99.032A,S99.032D-  
S99.032G,S99.039A,S99.039D-S99.039G,S99.041A,S99.041D-S99.041G,S99.042A,S99.042D-S99.042G,  
S99.049A,S99.049D-S99.049G,S99.091A,S99.091D-S99.091G,S99.092A,S99.092D-S99.092G,S99.099A,  
S99.099D-S99.099G,S99.101A,S99.101D-S99.101G,S99.102A,S99.102D-S99.102G,S99.109A,S99.109D-  
S99.109G,S99.111A,S99.111D-S99.111G,S99.112A,S99.112D-S99.112G,S99.119A,S99.119D-S99.119G,  
S99.121A,S99.121D-S99.121G,S99.122A,S99.122D-S99.122G,S99.129A,S99.129D-S99.129G,S99.131A,  
S99.131D-S99.131G,S99.132A,S99.132D-S99.132G,S99.139A,S99.139D-S99.139G,S99.141A,S99.141D-  
S99.141G,S99.142A,S99.142D-S99.142G,S99.149A,S99.149D-S99.149G,S99.191A,S99.191D-S99.191G,  
S99.192A,S99.192D-S99.192G,S99.199A,S99.199D-S99.199G,Z47.2  
CPT: 11740,20650,20670-20694,23470,23500-23515,23570-23630,24130,24500-24587,24620,24635,24650-24685,  
25119,25210-25240,25259,25320,25337-25393,25440-25447,25450-25652,25671,25800-25830,26520,26600-  
26615,26645-26665,26676,26720-26770,27130,27175-27181,27230-27235,27244,27245,27350,27409,27424,  
27430,27435,27465-27468,27500-27540,27570,27610,27620,27656,27664,27712,27750-27829,27846,27848,  
28300,28400-28531,28730,29049-29105,29126-29131,29240,29305-29445,29505,29515,29700-29720,29850-  
29856,29874-29879,29882,29894,29897-29899,93792,93793,97012,97018,97110-97124,97140-97168,97530,  
97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-  
99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,  
G0513,G0514

**Line: 356**  
Condition: RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, OSTEOCHONDRITIS DISSECCANS, AND ASEPTIC NECROSIS  
OF BONE (See Coding Specification Below) (See Guideline Notes 6,15,64,65,71,83,114,158)  
Treatment: ARTHROPLASTY/RECONSTRUCTION  
ICD-10: L40.50-L40.59,M02.10,M02.111-M02.19,M02.30,M02.311-M02.89,M05.611-M05.9,M06.00,M06.011-M06.29,  
M06.311-M06.39,M06.80,M06.811-M06.9,M08.00,M08.011-M08.48,M08.811-M08.99,M12.50,M12.511-M12.59,  
M13.871-M13.879,M16.0,M16.10-M16.9,M17.0,M17.10-M17.9,M18.0,M18.10-M18.9,M19.011-M19.93,M20.20-  
M20.22,M24.151-M24.176,M24.871-M24.872,M24.874-M24.875,M25.00,M25.011-M25.076,M25.151-M25.159,  
M25.851-M25.859,M25.871-M25.879,M76.20-M76.22,M87.00,M87.011-M87.9,M90.50,M90.511-M90.59,M93.20,  
M93.211-M93.29  
CPT: 20610,20611,20690-20694,23120,23470-23474,23800,23802,24000,24006,24101,24102,24130,24160,24164,  
24360-24371,24800,24802,25000,25101-25109,25115-25119,25210-25240,25270,25320,25337,25390-25393,  
25441-25492,25800,25810-25830,26320,26516-26536,26820-26863,26990-26992,27036,27090,27091,27122-  
27132,27187,27284,27286,27358,27437-27454,27457,27580,27620-27626,27641,27700-27704,27870,27871,  
28090,28104,28114,28116,28122,28289-28292,28446,28715,28725,28740,28750,29819-29826,29834-29838,  
29843-29848,29861-29863,29871-29876,29884-29887,29891,29892,29894-29899,29904-29916,77014,77261-  
77290,77295,77300,77306,77307,77331-77336,77385-77387,77401-77423,77427,77470,93792,93793,97012,  
97018,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,  
99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-  
99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,  
G0513,G0514,G6001-G6017,S2118,S2325

Knee arthroscopy (29871, 29873-29876, 29884-29887) is not included on this line when paired with  
osteoarthritis/osteoarthrosis of the knee (M17.0-M17.9).



PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

**Line: 357**  
Condition: CONDITIONS OF PULMONARY ARTERY (See Guideline Notes 64,65)  
Treatment: SURGICAL TREATMENT  
ICD-10: I28.0-I28.9, S25.401A-S25.401D, S25.402A-S25.402D, S25.409A-S25.409D, S25.411A-S25.411D, S25.412A-S25.412D, S25.419A-S25.419D, S25.421A-S25.421D, S25.422A-S25.422D, S25.429A-S25.429D, S25.491A-S25.491D, S25.492A-S25.492D, S25.499A-S25.499D  
CPT: 32480-32488, 32501, 32505-32540, 32663, 32666-32670, 33726, 33917-33922, 92960-92971, 92978-92998, 93792-93798, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0157-G0161, G0248-G0250, G0396, G0397, G0406-G0408, G0422, G0423, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514

**Line: 358**  
Condition: BODY INFESTATIONS (E.G., LICE, SCABIES) (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: B83.4, B85.0-B85.4, B86, B87.0-B87.4, B87.81-B87.9, B88.0-B88.9  
CPT: 93792, 93793, 96900, 96902, 96910-96913, 98966-98969, 99051, 99060, 99070, 99078, 99201-99215, 99281-99285, 99341-99378, 99381-99404, 99408-99449, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0463-G0467, G0490, G0511, G0513, G0514

**Line: 359**  
Condition: DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS (See Guideline Notes 6,64,65)  
Treatment: SURGICAL TREATMENT  
ICD-10: M22.00-M22.12, M24.00, M24.011-M24.073, M24.171-M24.176, M24.321-M24.376, M24.411-M24.443, M24.451-M24.476, M24.811-M24.812, M24.821-M24.822, M24.831-M24.832, M24.841-M24.842, M24.851-M24.852, M24.871-M24.872, M24.874-M24.875, M25.871-M25.879, M72.0, M92.40-M92.52, Q66.0-Q66.1, Q66.21-Q66.4, Q66.6-Q66.7, Q68.2, Q69.0-Q69.1, Q70.00-Q70.13, Q71.40-Q71.63, Q71.811-Q71.93, Q72.40-Q72.73, Q72.811-Q72.93, Q73.1-Q73.8, Q74.0, S03.00XA-S03.00XD, S03.01XA-S03.01XD, S03.02XA-S03.02XD, S03.03XA-S03.03XD, S33.30XA-S33.30XD, S33.39XA-S33.39XD, S43.001A-S43.001D, S43.002A-S43.002D, S43.003A-S43.003D, S43.004A-S43.004D, S43.005A-S43.005D, S43.006A-S43.006D, S43.011A-S43.011D, S43.012A-S43.012D, S43.013A-S43.013D, S43.014A-S43.014D, S43.015A-S43.015D, S43.016A-S43.016D, S43.021A-S43.021D, S43.022A-S43.022D, S43.023A-S43.023D, S43.024A-S43.024D, S43.025A-S43.025D, S43.026A-S43.026D, S43.031A-S43.031D, S43.032A-S43.032D, S43.033A-S43.033D, S43.034A-S43.034D, S43.035A-S43.035D, S43.036A-S43.036D, S43.081A-S43.081D, S43.082A-S43.082D, S43.083A-S43.083D, S43.084A-S43.084D, S43.085A-S43.085D, S43.086A-S43.086D, S43.101A-S43.101D, S43.102A-S43.102D, S43.109A-S43.109D, S43.111A-S43.111D, S43.112A-S43.112D, S43.119A-S43.119D, S43.121A-S43.121D, S43.122A-S43.122D, S43.129A-S43.129D, S43.131A-S43.131D, S43.132A-S43.132D, S43.139A-S43.139D, S43.141A-S43.141D, S43.142A-S43.142D, S43.149A-S43.149D, S43.151A-S43.151D, S43.152A-S43.152D, S43.159A-S43.159D, S43.201A-S43.201D, S43.202A-S43.202D, S43.203A-S43.203D, S43.204A-S43.204D, S43.205A-S43.205D, S43.206A-S43.206D, S43.211A-S43.211D, S43.212A-S43.212D, S43.213A-S43.213D, S43.214A-S43.214D, S43.215A-S43.215D, S43.216A-S43.216D, S43.221A-S43.221D, S43.222A-S43.222D, S43.223A-S43.223D, S43.224A-S43.224D, S43.225A-S43.225D, S43.226A-S43.226D, S43.301A-S43.301D, S43.302A-S43.302D, S43.303A-S43.303D, S43.304A-S43.304D, S43.305A-S43.305D, S43.306A-S43.306D, S43.311A-S43.311D, S43.312A-S43.312D, S43.313A-S43.313D, S43.314A-S43.314D, S43.315A-S43.315D, S43.316A-S43.316D, S43.391A-S43.391D, S43.392A-S43.392D, S43.393A-S43.393D, S43.394A-S43.394D, S43.395A-S43.395D, S43.396A-S43.396D, S53.001A-S53.001D, S53.002A-S53.002D, S53.003A-S53.003D, S53.004A-S53.004D, S53.005A-S53.005D, S53.006A-S53.006D, S53.011A-S53.011D, S53.012A-S53.012D, S53.013A-S53.013D, S53.014A-S53.014D, S53.015A-S53.015D, S53.016A-S53.016D, S53.021A-S53.021D, S53.022A-S53.022D, S53.023A-S53.023D, S53.024A-S53.024D, S53.025A-S53.025D, S53.026A-S53.026D, S53.031A-S53.031D, S53.032A-S53.032D, S53.033A-S53.033D, S53.091A-S53.091D, S53.092A-S53.092D, S53.093A-S53.093D, S53.094A-S53.094D, S53.095A-S53.095D, S53.096A-S53.096D, S53.101A-S53.101D, S53.102A-S53.102D, S53.103A-S53.103D, S53.104A-S53.104D, S53.105A-S53.105D, S53.106A-S53.106D, S53.111A-S53.111D, S53.112A-S53.112D, S53.113A-S53.113D, S53.114A-S53.114D, S53.115A-S53.115D, S53.116A-S53.116D, S53.121A-S53.121D, S53.122A-S53.122D, S53.123A-S53.123D, S53.124A-S53.124D, S53.125A-S53.125D, S53.126A-S53.126D, S53.131A-S53.131D, S53.132A-S53.132D, S53.133A-S53.133D, S53.134A-S53.134D, S53.135A-S53.135D, S53.136A-S53.136D, S53.141A-S53.141D, S53.142A-S53.142D, S53.143A-S53.143D, S53.144A-S53.144D, S53.145A-S53.145D, S53.146A-S53.146D, S53.191A-S53.191D, S53.192A-S53.192D, S53.193A-S53.193D, S53.194A-S53.194D, S53.195A-S53.195D, S53.196A-S53.196D, S63.001A-S63.001D, S63.002A-S63.002D, S63.003A-S63.003D, S63.004A-S63.004D, S63.005A-S63.005D, S63.006A-S63.006D, S63.011A-S63.011D, S63.012A-S63.012D, S63.013A-S63.013D, S63.014A-S63.014D, S63.015A-S63.015D, S63.016A-S63.016D, S63.021A-S63.021D, S63.022A-S63.022D, S63.023A-S63.023D, S63.024A-S63.024D, S63.025A-S63.025D, S63.026A-S63.026D, S63.031A-S63.031D, S63.032A-S63.032D, S63.033A-S63.033D, S63.034A-S63.034D, S63.035A-S63.035D, S63.036A-S63.036D, S63.041A-S63.041D, S63.042A-S63.042D, S63.043A-S63.043D, S63.044A-S63.044D, S63.045A-S63.045D, S63.046A-S63.046D, S63.051A-S63.051D, S63.052A-S63.052D, S63.053A-S63.053D, S63.054A-S63.054D, S63.055A-S63.055D, S63.056A-S63.056D, S63.061A-S63.061D, S63.062A-S63.062D, S63.063A-S63.063D, S63.064A-S63.064D, S63.065A-S63.065D, S63.066A-S63.066D, S63.071A-S63.071D, S63.072A-S63.072D, S63.073A-S63.073D, S63.074A-S63.074D, S63.075A-S63.075D, S63.076A-S63.076D, S63.091A-S63.091D, S63.092A-S63.092D, S63.093A-S63.093D, S63.094A-S63.094D, S63.095A-S63.095D, S63.096A-S63.096D, S63.101A-S63.101D, S63.102A-S63.102D, S63.103A-S63.103D, S63.104A-S63.104D, S63.105A-S63.105D, S63.106A-S63.106D, S63.111A-S63.111D, S63.112A-



PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

S63.112D,S63.113A-S63.113D,S63.114A-S63.114D,S63.115A-S63.115D,S63.116A-S63.116D,S63.121A-S63.121D,S63.122A-S63.122D,S63.123A-S63.123D,S63.124A-S63.124D,S63.125A-S63.125D,S63.126A-S63.126D,S63.200A-S63.200D,S63.201A-S63.201D,S63.202A-S63.202D,S63.203A-S63.203D,S63.204A-S63.204D,S63.205A-S63.205D,S63.206A-S63.206D,S63.207A-S63.207D,S63.208A-S63.208D,S63.209A-S63.209D,S63.210A-S63.210D,S63.211A-S63.211D,S63.212A-S63.212D,S63.213A-S63.213D,S63.214A-S63.214D,S63.215A-S63.215D,S63.216A-S63.216D,S63.217A-S63.217D,S63.218A-S63.218D,S63.219A-S63.219D,S63.220A-S63.220D,S63.221A-S63.221D,S63.222A-S63.222D,S63.223A-S63.223D,S63.224A-S63.224D,S63.225A-S63.225D,S63.226A-S63.226D,S63.227A-S63.227D,S63.228A-S63.228D,S63.229A-S63.229D,S63.230A-S63.230D,S63.231A-S63.231D,S63.232A-S63.232D,S63.233A-S63.233D,S63.234A-S63.234D,S63.235A-S63.235D,S63.236A-S63.236D,S63.237A-S63.237D,S63.238A-S63.238D,S63.239A-S63.239D,S63.240A-S63.240D,S63.241A-S63.241D,S63.242A-S63.242D,S63.243A-S63.243D,S63.244A-S63.244D,S63.245A-S63.245D,S63.246A-S63.246D,S63.247A-S63.247D,S63.248A-S63.248D,S63.249A-S63.249D,S63.250A-S63.250D,S63.251A-S63.251D,S63.252A-S63.252D,S63.253A-S63.253D,S63.254A-S63.254D,S63.255A-S63.255D,S63.256A-S63.256D,S63.257A-S63.257D,S63.258A-S63.258D,S63.259A-S63.259D,S63.260A-S63.260D,S63.261A-S63.261D,S63.262A-S63.262D,S63.263A-S63.263D,S63.264A-S63.264D,S63.265A-S63.265D,S63.266A-S63.266D,S63.267A-S63.267D,S63.268A-S63.268D,S63.269A-S63.269D,S63.270A-S63.270D,S63.271A-S63.271D,S63.272A-S63.272D,S63.273A-S63.273D,S63.274A-S63.274D,S63.275A-S63.275D,S63.276A-S63.276D,S63.277A-S63.277D,S63.278A-S63.278D,S63.279A-S63.279D,S63.280A-S63.280D,S63.281A-S63.281D,S63.282A-S63.282D,S63.283A-S63.283D,S63.284A-S63.284D,S63.285A-S63.285D,S63.286A-S63.286D,S63.287A-S63.287D,S63.288A-S63.288D,S63.289A-S63.289D,S63.290A-S63.290D,S63.291A-S63.291D,S63.292A-S63.292D,S63.293A-S63.293D,S63.294A-S63.294D,S63.295A-S63.295D,S63.296A-S63.296D,S63.297A-S63.297D,S63.298A-S63.298D,S63.299A-S63.299D,S73.001A-S73.001D,S73.002A-S73.002D,S73.003A-S73.003D,S73.004A-S73.004D,S73.005A-S73.005D,S73.006A-S73.006D,S73.011A-S73.011D,S73.012A-S73.012D,S73.013A-S73.013D,S73.014A-S73.014D,S73.015A-S73.015D,S73.016A-S73.016D,S73.021A-S73.021D,S73.022A-S73.022D,S73.023A-S73.023D,S73.024A-S73.024D,S73.025A-S73.025D,S73.026A-S73.026D,S73.031A-S73.031D,S73.032A-S73.032D,S73.033A-S73.033D,S73.034A-S73.034D,S73.035A-S73.035D,S73.036A-S73.036D,S73.041A-S73.041D,S73.042A-S73.042D,S73.043A-S73.043D,S73.044A-S73.044D,S73.045A-S73.045D,S73.046A-S73.046D,S83.001A-S83.001D,S83.002A-S83.002D,S83.003A-S83.003D,S83.004A-S83.004D,S83.005A-S83.005D,S83.006A-S83.006D,S83.011A-S83.011D,S83.012A-S83.012D,S83.013A-S83.013D,S83.014A-S83.014D,S83.015A-S83.015D,S83.016A-S83.016D,S83.091A-S83.091D,S83.092A-S83.092D,S83.093A-S83.093D,S83.094A-S83.094D,S83.095A-S83.095D,S83.096A-S83.096D,S83.101A-S83.101D,S83.102A-S83.102D,S83.103A-S83.103D,S83.104A-S83.104D,S83.105A-S83.105D,S83.106A-S83.106D,S83.111A-S83.111D,S83.112A-S83.112D,S83.113A-S83.113D,S83.114A-S83.114D,S83.115A-S83.115D,S83.116A-S83.116D,S83.121A-S83.121D,S83.122A-S83.122D,S83.123A-S83.123D,S83.124A-S83.124D,S83.125A-S83.125D,S83.126A-S83.126D,S83.131A-S83.131D,S83.132A-S83.132D,S83.133A-S83.133D,S83.134A-S83.134D,S83.135A-S83.135D,S83.136A-S83.136D,S83.141A-S83.141D,S83.142A-S83.142D,S83.143A-S83.143D,S83.144A-S83.144D,S83.145A-S83.145D,S83.146A-S83.146D,S83.191A-S83.191D,S83.192A-S83.192D,S83.193A-S83.193D,S83.194A-S83.194D,S83.195A-S83.195D,S83.196A-S83.196D,S93.01XA-S93.01XD,S93.02XA-S93.02XD,S93.03XA-S93.03XD,S93.04XA-S93.04XD,S93.05XA-S93.05XD,S93.06XA-S93.06XD,S93.101A-S93.101D,S93.102A-S93.102D,S93.103A-S93.103D,S93.104A-S93.104D,S93.105A-S93.105D,S93.106A-S93.106D,S93.111A-S93.111D,S93.112A-S93.112D,S93.113A-S93.113D,S93.114A-S93.114D,S93.115A-S93.115D,S93.116A-S93.116D,S93.119A-S93.119D,S93.121A-S93.121D,S93.122A-S93.122D,S93.123A-S93.123D,S93.124A-S93.124D,S93.125A-S93.125D,S93.126A-S93.126D,S93.129A-S93.129D,S93.131A-S93.131D,S93.132A-S93.132D,S93.133A-S93.133D,S93.134A-S93.134D,S93.135A-S93.135D,S93.136A-S93.136D,S93.139A-S93.139D,S93.141A-S93.141D,S93.142A-S93.142D,S93.143A-S93.143D,S93.144A-S93.144D,S93.145A-S93.145D,S93.146A-S93.146D,S93.149A-S93.149D,S93.301A-S93.301D,S93.302A-S93.302D,S93.303A-S93.303D,S93.304A-S93.304D,S93.305A-S93.305D,S93.306A-S93.306D,S93.311A-S93.311D,S93.312A-S93.312D,S93.313A-S93.313D,S93.314A-S93.314D,S93.315A-S93.315D,S93.316A-S93.316D,S93.321A-S93.321D,S93.322A-S93.322D,S93.323A-S93.323D,S93.324A-S93.324D,S93.325A-S93.325D,S93.326A-S93.326D,S93.331A-S93.331D,S93.332A-S93.332D,S93.333A-S93.333D,S93.334A-S93.334D,S93.335A-S93.335D,S93.336A-S93.336D,Z47.1

CPT: 11200,20527,20690-20694,21480,23455,23462-23470,23520-23552,23650-23700,24000,24006,24101,24102,24300,24332,24343,24345,24346,24600-24640,25001,25101-25109,25259,25275,25320,25335,25337,25390-25394,25430,25431,25441-25445,25447,25450-25492,25660-25695,25810-25830,26035,26040,26121-26180,26320-26341,26390,26440-26596,26641-26715,26770-26863,26951,27033,27097,27100-27122,27138-27170,27179,27185,27250-27258,27265,27266,27269,27275,27306,27307,27350,27420-27495,27550-27598,27603-27612,27615,27618-27630,27634-27692,27698,27705,27715,27727-27742,27829-27860,28008-28035,28043-28072,28086-28092,28110-28118,28126-28160,28220-28280,28288,28300-28305,28307-28341,28360,28540-28730,28737-28760,29049-29105,29126-29131,29305-29515,29700-29720,29750,29806-29819,29822,29823,29828,29834,29861-29863,29873,29874,29881,29882,29891,29892,29894,29904-29907,64702,64704,93792,93793,97012,97018,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: D7810-D7830,G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S2115



**PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)**

- Line: 360**  
Condition: CHORIORETINAL INFLAMMATION (See Guideline Notes 10,64,65,116)  
Treatment: MEDICAL, SURGICAL, AND LASER TREATMENT  
ICD-10: A50.01,A50.30,A50.39,A51.43,A52.71,B58.00,B58.09,H20.821-H20.829,H30.001-H30.93,H31.21,H32,H44.111-H44.119,H44.131-H44.139  
CPT: 67027,67028,67036-67043,67208,67210,67220,67227-67229,67515,92002-92014,92018-92060,92081-92136,92225-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 361**  
Condition: SCOLIOSIS (See Guideline Notes 41,56,60,64,65,92,100)  
Treatment: MEDICAL AND SURGICAL THERAPY  
ICD-10: M41.00-M41.08,M41.112-M41.9,M96.5,Q67.5,Q76.3,Z47.82  
CPT: 20660-20665,20930-20938,21720,21725,22206-22226,22532-22855,22859,29000-29046,29710,29720,62287,63001-63091,63170,63180-63199,63295-63610,63650,63655,63685,93792,93793,96150-96155,97110-97124,97140-97168,97530,97535,97760,97763,97810-98942,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487,99489,99495,99496,99605-99607  
HCPCS: G0157-G0160,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0508-G0511,G0513,G0514
- Line: 362**  
Condition: DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM (See Coding Specification Below) (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: G10,G21.0,G23.0-G23.9,G24.02-G24.3,G24.5-G24.9,G25.0-G25.5,G25.61-G25.69,G25.9,G80.3,G90.3,J38.5  
CPT: 31513,31570,31571,31573,31641,64612,64616,93792,93793,95873,95874,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Chemodenervation with botulinum toxin injection (CPT 64612, 64616) is included on this line only for treatment of blepharospasm (ICD-10-CM G24.5), spasmodic torticollis (ICD-10-CM G24.3), and other fragments of torsion dystonia (ICD-10-CM G24.9)
- Line: 363**  
Condition: CYST AND PSEUDOCYST OF PANCREAS (See Guideline Notes 64,65)  
Treatment: DRAINAGE OF PANCREATIC CYST  
ICD-10: K86.2-K86.3  
CPT: 43240,43274-43276,48000-48020,48105-48148,48152-48154,48500-48540,48548,49322,49324,49325,49405,49421-49423,64680,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 364**  
Condition: ACUTE SINUSITIS (See Guideline Notes 64,65)  
Treatment: MEDICAL TREATMENT  
ICD-10: J01.00,J01.10,J01.20,J01.30,J01.40,J01.80,J01.90  
CPT: 31000,31002,31090,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514,S2342
- Line: 365**  
Condition: HYPHEMA  
Treatment: REMOVAL OF BLOOD CLOT  
ICD-10: H21.00-H21.03  
CPT: 65810,65815,65930,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514



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<b>Line:</b>	<b>366</b>
Condition:	ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (See Guideline Notes 64,65)
Treatment:	MEDICAL THERAPY
ICD-10:	B44.81
CPT:	32662,33405-33430,33973,33974,35180-35184,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>367</b>
Condition:	ENTROPION AND TRICHIASIS OF EYELID
Treatment:	REPAIR
ICD-10:	H02.001-H02.059
CPT:	67820-67850,67880,67882,67921-67924,67950-67975,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
<b>Line:</b>	<b>368</b>
Condition:	STREPTOCOCCAL SORE THROAT AND SCARLET FEVER; VINCENT'S DISEASE; ULCER OF TONSIL; UNILATERAL HYPERTROPHY OF TONSIL (See Guideline Notes 36,64,65)
Treatment:	MEDICAL THERAPY, TONSILLECTOMY/ADENOIDECTOMY
ICD-10:	A38.0-A38.9,A69.0-A69.1,J02.0,J03.00-J03.01,J35.1,J35.3-J35.8
CPT:	42820-42826,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>369</b>
Condition:	INTESTINAL PARASITES (See Guideline Notes 64,65)
Treatment:	MEDICAL THERAPY
ICD-10:	A07.2-A07.4,A07.9,B65.0-B65.9,B66.0-B66.9,B67.0-B67.2,B67.31-B67.99,B68.0,B72,B73.00-B73.1,B74.0-B74.9,B76.0-B76.9,B77.0,B77.81-B77.9,B78.0,B78.7-B78.9,B79-B80,B81.0-B81.8,B82.0-B82.9,B83.0-B83.3,B83.8-B83.9
CPT:	93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>370</b>
Condition:	AMBLYOPIA (See Guideline Notes 64,65)
Treatment:	MEDICAL AND SURGICAL TREATMENT
ICD-10:	H53.001-H53.039
CPT:	65778-65782,66820-66986,67311-67343,67901-67909,68135,68320-68328,68335,68340,68371,92002-92014,92018-92060,92081-92136,92225,92226,92230-92310,92314,92325-92342,92370,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>371</b>
Condition:	ENCEPHALOCELE
Treatment:	SURGICAL TREATMENT
ICD-10:	Q01.0-Q01.9
CPT:	20664,61020,61070,61107,61210,61215,61322,61323,62100,62120,62121,62160-62163,62180-62258,62272,63740-63746,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>372</b>
Condition:	BENIGN NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGANS (See Guideline Notes 12,16,64,65)
Treatment:	LOBECTOMY, MEDICAL THERAPY, WHICH INCLUDES RADIATION THERAPY
ICD-10:	D14.1-D14.2,D14.30-D14.4,D15.0-D15.9,D19.0,D3A.090-D3A.091,G89.3,Z51.0
CPT:	19260-19272,21627,21630,31512,31541-31546,31572,31592,31630,31631,31636-31641,31770,31775,32320,32480-32488,32505-32540,32553,32661-32663,32666-32670,32673,33120,33130,39000,39010,39220,49411,60520-60522,77014,77261-77290,77295,77306-77318,77331-77370,77385-77387,77402-77432,77469,77470,77600-77763,77770-77790,79005-79445,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017



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**Line: 373**  
Condition: ACNE CONGLOBATA (SEVERE CYSTIC ACNE) (See Guideline Notes 64,65,132)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: L70.0-L70.9,L73.0  
CPT: 10040-10061,11900,11901,17000,17340,17360,93792,93793,96900,96902,96910-96913,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 374**  
Condition: RETINAL TEAR (See Guideline Notes 64,65,171)  
Treatment: LASER PROPHYLAXIS  
ICD-10: H33.301-H33.339,H35.411-H35.419  
CPT: 67039,67141,67145,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 375**  
Condition: CHOLESTEATOMA; INFECTIONS OF THE PINNA (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: H60.40-H60.43,H61.001-H61.039,H70.811-H70.899,H71.00-H71.93,H74.11-H74.23,H74.311-H74.399,H95.00-H95.03,H95.121-H95.129  
CPT: 21235,69220,69420,69421,69433-69540,69601-69646,69662,69670,69700,69905,69910,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 376**  
Condition: DISRUPTIONS OF THE LIGAMENTS AND TENDONS OF THE ARMS AND LEGS, EXCLUDING THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT (See Guideline Notes 6,28,64,65,98,120)  
Treatment: REPAIR  
ICD-10: M12.00,M12.011-M12.09,M25.751-M25.759,M35.4,M62.10,M62.111-M62.28,M62.89,M65.311-M65.319,M66.0,M66.111-M66.18,M66.221-M66.259,M66.271-M66.80,M66.821-M66.89,M70.60-M70.72,M72.8,M76.00-M76.12,M76.30-M76.32,S53.20XA-S53.20XD,S53.21XA-S53.21XD,S53.22XA-S53.22XD,S53.30XA-S53.30XD,S53.31XA-S53.31XD,S53.32XA-S53.32XD,S53.401A-S53.401D,S53.402A-S53.402D,S53.409A-S53.409D,S53.411A-S53.411D,S53.412A-S53.412D,S53.419A-S53.419D,S53.421A-S53.421D,S53.422A-S53.422D,S53.429A-S53.429D,S53.431A-S53.431D,S53.432A-S53.432D,S53.439A-S53.439D,S53.441A-S53.441D,S53.442A-S53.442D,S53.449A-S53.449D,S53.491A-S53.491D,S53.492A-S53.492D,S53.499A-S53.499D,S56.011A-S56.011D,S56.012A-S56.012D,S56.019A-S56.019D,S56.111A-S56.111D,S56.112A-S56.112D,S56.113A-S56.113D,S56.114A-S56.114D,S56.115A-S56.115D,S56.116A-S56.116D,S56.117A-S56.117D,S56.118A-S56.118D,S56.119A-S56.119D,S56.211A-S56.211D,S56.212A-S56.212D,S56.219A-S56.219D,S56.311A-S56.311D,S56.312A-S56.312D,S56.319A-S56.319D,S56.411A-S56.411D,S56.412A-S56.412D,S56.413A-S56.413D,S56.414A-S56.414D,S56.415A-S56.415D,S56.416A-S56.416D,S56.417A-S56.417D,S56.418A-S56.418D,S56.419A-S56.419D,S56.511A-S56.511D,S56.512A-S56.512D,S56.519A-S56.519D,S56.811A-S56.811D,S56.812A-S56.812D,S56.819A-S56.819D,S56.911A-S56.911D,S56.912A-S56.912D,S56.919A-S56.919D,S63.301A-S63.301D,S63.302A-S63.302D,S63.309A-S63.309D,S63.311A-S63.311D,S63.312A-S63.312D,S63.319A-S63.319D,S63.321A-S63.321D,S63.322A-S63.322D,S63.329A-S63.329D,S63.331A-S63.331D,S63.332A-S63.332D,S63.339A-S63.339D,S63.391A-S63.391D,S63.392A-S63.392D,S63.399A-S63.399D,S63.400A-S63.400D,S63.401A-S63.401D,S63.402A-S63.402D,S63.403A-S63.403D,S63.404A-S63.404D,S63.405A-S63.405D,S63.406A-S63.406D,S63.407A-S63.407D,S63.408A-S63.408D,S63.409A-S63.409D,S63.410A-S63.410D,S63.411A-S63.411D,S63.412A-S63.412D,S63.413A-S63.413D,S63.414A-S63.414D,S63.415A-S63.415D,S63.416A-S63.416D,S63.417A-S63.417D,S63.418A-S63.418D,S63.419A-S63.419D,S63.420A-S63.420D,S63.421A-S63.421D,S63.422A-S63.422D,S63.423A-S63.423D,S63.424A-S63.424D,S63.425A-S63.425D,S63.426A-S63.426D,S63.427A-S63.427D,S63.428A-S63.428D,S63.429A-S63.429D,S63.430A-S63.430D,S63.431A-S63.431D,S63.432A-S63.432D,S63.433A-S63.433D,S63.434A-S63.434D,S63.435A-S63.435D,S63.436A-S63.436D,S63.437A-S63.437D,S63.438A-S63.438D,S63.439A-S63.439D,S63.490A-S63.490D,S63.491A-S63.491D,S63.492A-S63.492D,S63.493A-S63.493D,S63.494A-S63.494D,S63.495A-S63.495D,S63.496A-S63.496D,S63.497A-S63.497D,S63.498A-S63.498D,S63.499A-S63.499D,S63.501A-S63.501D,S63.502A-S63.502D,S63.509A-S63.509D,S63.511A-S63.511D,S63.512A-S63.512D,S63.519A-S63.519D,S63.521A-S63.521D,S63.522A-S63.522D,S63.529A-S63.529D,S63.591A-S63.591D,S63.592A-S63.592D,S63.599A-S63.599D,S63.601A-S63.601D,S63.602A-S63.602D,S63.609A-S63.609D,S63.610A-S63.610D,S63.611A-S63.611D,S63.612A-S63.612D,S63.613A-S63.613D,S63.614A-S63.614D,S63.615A-S63.615D,S63.616A-S63.616D,S63.617A-S63.617D,S63.618A-S63.618D,S63.619A-S63.619D,S63.621A-S63.621D,S63.622A-S63.622D,S63.629A-S63.629D,S63.630A-S63.630D,S63.631A-S63.631D,S63.632A-S63.632D,S63.633A-S63.633D,S63.634A-S63.634D,S63.635A-S63.635D,S63.636A-S63.636D,S63.637A-S63.637D,S63.638A-S63.638D,S63.639A-S63.639D,S63.641A-S63.641D,S63.642A-S63.642D,S63.649A-S63.649D,S63.650A-S63.650D,S63.651A-S63.651D,S63.652A-S63.652D,S63.653A-S63.653D,S63.654A-S63.654D,S63.655A-S63.655D,S63.656A-S63.656D,S63.657A-S63.657D,S63.658A-S63.658D,S63.659A-S63.659D,S63.681A-S63.681D,S63.682A-S63.682D,S63.689A-S63.689D,S63.690A-



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JANUARY 1, 2018 (REVISED)

S63.690D,S63.691A-S63.691D,S63.692A-S63.692D,S63.693A-S63.693D,S63.694A-S63.694D,S63.695A-S63.695D,S63.696A-S63.696D,S63.697A-S63.697D,S63.698A-S63.698D,S63.699A-S63.699D,S63.8X1A-S63.8X1D,S63.8X2A-S63.8X2D,S63.8X9A-S63.8X9D,S63.90XA-S63.90XD,S63.91XA-S63.91XD,S63.92XA-S63.92XD,S66.011A-S66.011D,S66.012A-S66.012D,S66.019A-S66.019D,S66.110A-S66.110D,S66.111A-S66.111D,S66.112A-S66.112D,S66.113A-S66.113D,S66.114A-S66.114D,S66.115A-S66.115D,S66.116A-S66.116D,S66.117A-S66.117D,S66.118A-S66.118D,S66.119A-S66.119D,S66.211A-S66.211D,S66.212A-S66.212D,S66.219A-S66.219D,S66.310A-S66.310D,S66.311A-S66.311D,S66.312A-S66.312D,S66.313A-S66.313D,S66.314A-S66.314D,S66.315A-S66.315D,S66.316A-S66.316D,S66.317A-S66.317D,S66.318A-S66.318D,S66.319A-S66.319D,S66.411A-S66.411D,S66.412A-S66.412D,S66.419A-S66.419D,S66.510A-S66.510D,S66.511A-S66.511D,S66.512A-S66.512D,S66.513A-S66.513D,S66.514A-S66.514D,S66.515A-S66.515D,S66.516A-S66.516D,S66.517A-S66.517D,S66.518A-S66.518D,S66.519A-S66.519D,S66.811A-S66.811D,S66.812A-S66.812D,S66.819A-S66.819D,S66.911A-S66.911D,S66.912A-S66.912D,S66.919A-S66.919D,S73.101A-S73.101D,S73.102A-S73.102D,S73.109A-S73.109D,S73.111A-S73.111D,S73.112A-S73.112D,S73.119A-S73.119D,S73.121A-S73.121D,S73.122A-S73.122D,S73.129A-S73.129D,S73.191A-S73.191D,S73.192A-S73.192D,S73.199A-S73.199D,S76.011A-S76.011D,S76.012A-S76.012D,S76.019A-S76.019D,S76.111A-S76.111D,S76.112A-S76.112D,S76.119A-S76.119D,S76.211A-S76.211D,S76.212A-S76.212D,S76.219A-S76.219D,S76.311A-S76.311D,S76.312A-S76.312D,S76.319A-S76.319D,S76.811A-S76.811D,S76.812A-S76.812D,S76.819A-S76.819D,S76.911A-S76.911D,S76.912A-S76.912D,S76.919A-S76.919D,S86.011A-S86.011D,S86.012A-S86.012D,S86.019A-S86.019D,S93.401A-S93.401D,S93.402A-S93.402D,S93.409A-S93.409D,S93.411A-S93.411D,S93.412A-S93.412D,S93.419A-S93.419D,S93.421A-S93.421D,S93.422A-S93.422D,S93.429A-S93.429D,S93.431A-S93.431D,S93.432A-S93.432D,S93.439A-S93.439D,S93.491A-S93.491D,S93.492A-S93.492D,S93.499A-S93.499D,S96.011A-S96.011D,S96.012A-S96.012D,S96.019A-S96.019D,S96.111A-S96.111D,S96.112A-S96.112D,S96.119A-S96.119D,S96.211A-S96.211D,S96.212A-S96.212D,S96.219A-S96.219D,S96.811A-S96.811D,S96.812A-S96.812D,S96.819A-S96.819D,S96.911A-S96.911D,S96.912A-S96.912D,S96.919A-S96.919D

CPT: 20550,20610,20611,23430,24340-24342,24344,25310,26055,26350-26412,26418,26420,26428-26437,26474,26480,26497,26530,26540,26775,26776,27380-27386,27650-27654,27658-27675,27695-27698,27829,28200-28210,29065-29105,29126-29280,29345-29425,29440,29445,29505-29540,29700,29705,29828,29861-29863,29901,29902,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 377**  
Condition: DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION (See Guideline Notes 6,38,64,65,90)  
Treatment: MEDICAL THERAPY (SHORT TERM REHABILITATION WITH DEFINED GOALS)  
ICD-10: A33,A50.40,A50.43,A50.45,A52.10-A52.19,A52.3,A81.00-A81.83,A87.1-A87.2,A88.8,A89,C70.0-C70.9,C71.0-C71.9,C72.0-C72.1,C72.20-C72.9,D33.9,D81.3,D81.5,E00.0-E00.9,E45,E70.0-E70.1,E70.20-E70.29,E70.320-E70.331,E70.39,E70.5-E70.9,E71.0,E71.110-E71.548,E72.00-E72.51,E72.59-E72.9,E74.00-E74.09,E74.20-E74.29,E75.00-E75.09,E75.11-E75.23,E75.240-E75.6,E76.01-E76.1,E76.210-E76.9,E77.0-E77.9,E78.70-E78.9,E79.1-E79.9,E80.0-E80.1,E80.20-E80.3,E83.00-E83.09,E88.2,E88.40-E88.49,E88.89,F01.50-F01.51,F03.90-F03.91,F06.1,F06.8,F07.89,F70-F79,F84.0-F84.3,F84.8,G04.1,G04.81-G04.91,G10,G11.0-G11.9,G12.0-G12.1,G12.21-G12.9,G13.1-G13.8,G14-G20,G21.0,G21.11-G21.9,G23.0-G23.9,G24.01,G24.1-G24.2,G24.8,G25.4-G25.5,G25.82,G25.9,G30.0-G30.8,G31.01-G31.9,G32.0,G32.81-G32.89,G35,G36.0-G36.9,G37.0-G37.9,G40.011-G40.019,G40.111-G40.119,G40.211-G40.219,G40.311-G40.319,G40.411-G40.419,G40.811,G40.89,G40.911-G40.919,G60.0-G60.8,G61.0-G61.1,G61.81-G61.89,G62.0-G62.2,G62.81-G62.89,G64,G71.0,G71.11-G71.8,G72.0-G72.3,G72.41-G72.89,G73.7,G80.0-G80.9,G81.00-G81.94,G82.20-G82.54,G83.0,G83.10-G83.9,G90.01-G90.1,G90.3-G90.4,G90.50,G90.511-G90.59,G91.0-G91.9,G92,G93.0-G93.1,G93.40-G93.81,G93.89,G94,G95.0,G95.11-G95.89,G97.0,G97.2,G97.31-G97.32,G97.48-G97.49,G97.61-G97.82,G98.0,G99.0-G99.8,H49.811-H49.819,H54.0X33-H54.3,H54.8,I61.0-I61.9,I62.00-I62.9,I63.30,I63.311-I63.312,I63.319-I63.322,I63.329-I63.332,I63.339-I63.342,I63.349-I63.412,I63.419-I63.422,I63.429-I63.432,I63.439-I63.442,I63.449-I63.512,I63.519-I63.522,I63.529-I63.532,I63.539-I63.542,I63.549-I63.9,I67.3,I67.81-I67.83,I67.841-I67.89,I69.010-I69.018,I69.020-I69.090,I69.092-I69.093,I69.110-I69.118,I69.120-I69.190,I69.192-I69.193,I69.210-I69.218,I69.220-I69.290,I69.292-I69.293,I69.310-I69.318,I69.320-I69.390,I69.392-I69.393,I69.810-I69.818,I69.820-I69.890,I69.892-I69.893,I69.910-I69.918,I69.920-I69.990,I69.992-I69.993,I97.810-I97.821,M14.60,M14.611-M14.69,M20.021-M20.099,M21.00,M21.021-M21.079,M21.121-M21.172,M21.20,M21.211-M21.379,M21.511-M21.529,M21.541-M21.549,M21.6X1-M21.969,M61.111-M61.112,M61.121-M61.122,M61.131-M61.132,M61.141-M61.142,M61.144-M61.145,M61.151-M61.152,M61.161-M61.162,M61.171-M61.172,M61.174-M61.175,M61.177-M61.178,M61.18-M61.19,M61.211-M61.212,M61.221-M61.222,M61.231-M61.232,M61.241-M61.242,M61.251-M61.252,M61.261-M61.262,M61.271-M61.272,M61.28-M61.29,M61.311-M61.312,M61.321-M61.322,M61.331-M61.332,M61.341-M61.342,M61.351-M61.352,M61.361-M61.362,M61.371-M61.372,M61.38-M61.39,M61.411-M61.412,M61.421-M61.422,M61.431-M61.432,M61.441-M61.442,M61.451-M61.452,M61.461-M61.462,M61.471-M61.472,M61.48-M61.49,M61.511-M61.512,M61.521-M61.522,M61.531-M61.532,M61.541-M61.542,M61.551-M61.552,M61.561-M61.562,M61.571-M61.572,M61.58-M61.59,M62.3,M62.511-M62.59,M62.89,P07.00-P07.39,P10.0-P10.9,P11.0,P11.2,P11.5-P11.9,P19.0-P19.9,P24.00-P24.21,P24.80-P24.9,P35.0-P35.9,P37.0-P37.9,P39.2,P50.0-P50.9,P51.0-P51.9,P52.0-P52.1,P52.21-P52.9,P54.1-P54.9,P55.1-P55.9,P56.0-P56.9,P56.99-P57.0,P91.2,P91.60-P91.63,P96.81,Q00.0-Q00.2,Q01.0-Q01.9,Q02,Q03.0-Q03.9,Q04.0-Q04.9,Q05.0-Q05.9,Q06.0-Q06.9,Q07.00-Q07.9,Q68.1,Q71.00-Q71.33,Q72.00-Q72.33,Q73.0,Q74.3,Q77.3,Q77.6,Q78.0-Q78.3,Q78.5-Q78.6,Q85.1,Q86.0-Q86.8,Q87.1-Q87.3,Q87.40,Q87.410-Q87.89,Q89.4-Q89.8,Q90.0-Q90.9,Q91.0-Q91.7,Q92.0-



*PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)*

Q92.5,Q92.62-Q92.9,Q93.0-Q93.7,Q93.81-Q93.9,Q95.2-Q95.8,Q96.0-Q96.9,Q97.0-Q97.8,Q98.0-Q98.3,Q98.5-Q98.8,Q99.0-Q99.8,R41.4,R41.81,R53.2,R54,S06.370A-S06.370D,S06.810A-S06.810D,S06.811A-S06.811D,S06.812A-S06.812D,S06.813A-S06.813D,S06.814A-S06.814D,S06.815A-S06.815D,S06.816A-S06.816D,S06.817A-S06.817D,S06.820A-S06.820D,S06.821A-S06.821D,S06.822A-S06.822D,S06.823A-S06.823D,S06.824A-S06.824D,S06.825A-S06.825D,S06.826A-S06.826D,S06.827A-S06.827D,S06.890A-S06.890D,S06.891A-S06.891D,S06.892A-S06.892D,S06.893A-S06.893D,S06.894A-S06.894D,S06.895A-S06.895D,S06.896A-S06.896D,S06.897A-S06.897D,S06.9X0A-S06.9X0D,S06.9X1A-S06.9X1D,S06.9X2A-S06.9X2D,S06.9X3A-S06.9X3D,S06.9X4A-S06.9X4D,S06.9X5A-S06.9X5D,S06.9X6A-S06.9X6D,S06.9X7A-S06.9X7D,S06.9X9A-S06.9X9D,S14.0XXA-S14.0XXD,S14.101A-S14.101D,S14.102A-S14.102D,S14.103A-S14.103D,S14.104A-S14.104D,S14.105A-S14.105D,S14.106A-S14.106D,S14.107A-S14.107D,S14.108A-S14.108D,S14.109A-S14.109D,S14.111A-S14.111D,S14.112A-S14.112D,S14.113A-S14.113D,S14.114A-S14.114D,S14.115A-S14.115D,S14.116A-S14.116D,S14.117A-S14.117D,S14.118A-S14.118D,S14.119A-S14.119D,S14.121A-S14.121D,S14.122A-S14.122D,S14.123A-S14.123D,S14.124A-S14.124D,S14.125A-S14.125D,S14.126A-S14.126D,S14.127A-S14.127D,S14.128A-S14.128D,S14.129A-S14.129D,S14.131A-S14.131D,S14.132A-S14.132D,S14.133A-S14.133D,S14.134A-S14.134D,S14.135A-S14.135D,S14.136A-S14.136D,S14.137A-S14.137D,S14.138A-S14.138D,S14.139A-S14.139D,S14.141A-S14.141D,S14.142A-S14.142D,S14.143A-S14.143D,S14.144A-S14.144D,S14.145A-S14.145D,S14.146A-S14.146D,S14.147A-S14.147D,S14.148A-S14.148D,S14.149A-S14.149D,S14.151A-S14.151D,S14.152A-S14.152D,S14.153A-S14.153D,S14.154A-S14.154D,S14.155A-S14.155D,S14.156A-S14.156D,S14.157A-S14.157D,S14.158A-S14.158D,S14.159A-S14.159D,S14.2XXA-S14.2XXD,S14.3XXA-S14.3XXD,S24.0XXA-S24.0XXD,S24.101A-S24.101D,S24.102A-S24.102D,S24.103A-S24.103D,S24.104A-S24.104D,S24.109A-S24.109D,S24.111A-S24.111D,S24.112A-S24.112D,S24.113A-S24.113D,S24.114A-S24.114D,S24.119A-S24.119D,S24.131A-S24.131D,S24.132A-S24.132D,S24.133A-S24.133D,S24.134A-S24.134D,S24.139A-S24.139D,S24.141A-S24.141D,S24.142A-S24.142D,S24.143A-S24.143D,S24.144A-S24.144D,S24.149A-S24.149D,S24.151A-S24.151D,S24.152A-S24.152D,S24.153A-S24.153D,S24.154A-S24.154D,S24.159A-S24.159D,S24.2XXA-S24.2XXD,S34.01XA-S34.01XD,S34.02XA-S34.02XD,S34.101A-S34.101D,S34.102A-S34.102D,S34.103A-S34.103D,S34.104A-S34.104D,S34.105A-S34.105D,S34.109A-S34.109D,S34.111A-S34.111D,S34.112A-S34.112D,S34.113A-S34.113D,S34.114A-S34.114D,S34.115A-S34.115D,S34.119A-S34.119D,S34.121A-S34.121D,S34.122A-S34.122D,S34.123A-S34.123D,S34.124A-S34.124D,S34.125A-S34.125D,S34.129A-S34.129D,S34.131A-S34.131D,S34.132A-S34.132D,S34.139A-S34.139D,S34.21XA-S34.21XD,S34.22XA-S34.22XD,S34.3XXA-S34.3XXD,S34.4XXA-S34.4XXD,T40.0X1A-T40.0X1D,T40.0X2A-T40.0X2D,T40.0X3A-T40.0X3D,T40.0X4A-T40.0X4D,T40.1X1A-T40.1X1D,T40.1X2A-T40.1X2D,T40.1X3A-T40.1X3D,T40.1X4A-T40.1X4D,T40.2X1A-T40.2X1D,T40.2X2A-T40.2X2D,T40.2X3A-T40.2X3D,T40.2X4A-T40.2X4D,T40.3X1A-T40.3X1D,T40.3X2A-T40.3X2D,T40.3X3A-T40.3X3D,T40.3X4A-T40.3X4D,T40.4X1A-T40.4X1D,T40.4X2A-T40.4X2D,T40.4X3A-T40.4X3D,T40.4X4A-T40.4X4D,T40.5X1A-T40.5X1D,T40.5X2A-T40.5X2D,T40.5X3A-T40.5X3D,T40.5X4A-T40.5X4D,T40.601A-T40.601D,T40.602A-T40.602D,T40.603A-T40.603D,T40.604A-T40.604D,T40.691A-T40.691D,T40.692A-T40.692D,T40.693A-T40.693D,T40.694A-T40.694D,T40.7X1A-T40.7X1D,T40.7X2A-T40.7X2D,T40.7X3A-T40.7X3D,T40.7X4A-T40.7X4D,T40.8X1A-T40.8X1D,T40.8X2A-T40.8X2D,T40.8X3A-T40.8X3D,T40.8X4A-T40.8X4D,T40.901A-T40.901D,T40.902A-T40.902D,T40.903A-T40.903D,T40.904A-T40.904D,T40.991A-T40.991D,T71.111A-T71.111D,T71.112A-T71.112D,T71.113A-T71.113D,T71.114A-T71.114D,T71.121A-T71.121D,T71.122A-T71.122D,T71.123A-T71.123D,T71.124A-T71.124D,T71.131A-T71.131D,T71.132A-T71.132D,T71.133A-T71.133D,T71.134A-T71.134D,T71.141A-T71.141D,T71.143A-T71.143D,T71.144A-T71.144D,T71.151A-T71.151D,T71.152A-T71.152D,T71.153A-T71.153D,T71.154A-T71.154D,T71.161A-T71.161D,T71.162A-T71.162D,T71.163A-T71.163D,T71.164A-T71.164D,T71.191A-T71.191D,T71.192A-T71.192D,T71.193A-T71.193D,T71.194A-T71.194D,T71.20XA-T71.20XD,T71.21XA-T71.21XD,T71.221A-T71.221D,T71.222A-T71.222D,T71.223A-T71.223D,T71.224A-T71.224D,T71.231A-T71.231D,T71.232A-T71.232D,T71.233A-T71.233D,T71.234A-T71.234D,T71.29XA-T71.29XD,T71.9XXA-T71.9XXD,T74.4XXA-T74.4XXD,T75.01XA-T75.01XD,T75.09XA-T75.09XD,T75.1XXA-T75.1XXD,T75.4XXA-T75.4XXD,T78.00XA-T78.00XD,T78.01XA-T78.01XD,T78.02XA-T78.02XD,T78.03XA-T78.03XD,T78.04XA-T78.04XD,T78.05XA-T78.05XD,T78.06XA-T78.06XD,T78.07XA-T78.07XD,T78.08XA-T78.08XD,T78.09XA-T78.09XD,T78.3XXA-T78.3XXD,T78.8XXA-T78.8XXD,T79.0XXA-T79.0XXD,T79.4XXA-T79.4XXD,T79.6XXA-T79.6XXD,T88.2XXA-T88.2XXD,T88.51XA-T88.51XD,T88.6XXA-T88.6XXD,Z44.001-Z44.22,Z44.8,Z46.

CPT: 61215,92002-92014,92083,93792,93793,96150-96155,97012,97110-97127,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0428-G0429,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,  
G0513-G0515,S2117

<b>Line:</b>	<b>378</b>
Condition:	ESOPHAGEAL STRICTURE; ACHALASIA (See Coding Specification Below) (See Guideline Notes 64,65)
Treatment:	MEDICAL AND SURGICAL TREATMENT
ICD-10:	K20.0,K22.0,K22.2,Z46.59
CPT:	32110-32124,32820,43192,43195,43196,43201,43212-43214,43220,43226,43229,43233,43248,43249,43266,43279,43330,43410-43453,44300,49442,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

Chemodenervation with botulinum toxin injection (CPT 43201) is included on this line for treatment of achalasia (ICD-10 K22.0)



**PRIORITIZED LIST OF HEALTH SERVICES  
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- Line: 379**  
Condition: CHRONIC ULCER OF SKIN (See Guideline Notes 62,64,65,163)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: E08.621-E08.622,E09.621-E09.622,E10.621-E10.622,E11.621-E11.622,E13.621-E13.622,I70.231-I70.25,I70.331-I70.35,I70.431-I70.45,I70.531-I70.55,I70.631-I70.65,I70.731-I70.75,I83.001-I83.029,I83.201-I83.229,I87.011-I87.019,I87.031-I87.039,I87.311-I87.319,I87.331-I87.339,L88,L89.000-L89.95,L97.101-L97.929,L98.411-L98.499  
CPT: 10060,10061,11000-11047,13101,13102,14350-15005,15271-15278,15920-15958,27598,27880,27881,27884-27888,28120,28122,28800-28825,29445,29580-29584,36465,36466,36470-36479,37700-37785,93792,93793,96150-96155,97605-97608,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: D7920,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 380**  
Condition: ESOPHAGITIS; GERD (See Guideline Note 144)  
Treatment: SHORT-TERM MEDICAL THERAPY; SURGICAL TREATMENT  
ICD-10: K20.8-K20.9,K21.0-K21.9,K22.5,K22.70,K22.710  
CPT: 43030,43130-43180,43192,43201,43210,43227,43279-43282,43327-43337,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 381**  
Condition: BULIMIA NERVOSA AND UNSPECIFIED EATING DISORDERS (See Coding Specification Below) (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F50.2,F50.81,F50.89-F50.9  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,97802-97804,98966-98969,99051,99060,99201-99239,99304-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005
- ICD-10 F50.89 is included on Line 381 for psychogenic loss of appetite. ICD-10 F50.89 is included on Line 629 for pica in adults and for all other diagnoses using this code.
- Line: 382**  
Condition: LATE SYPHILIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A52.10-A52.15,A52.19-A52.9,A53.0-A53.9  
CPT: 47015,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 383**  
Condition: CENTRAL SEROUS CHORIORETINOPATHY (See Coding Specification Below) (See Guideline Notes 10,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: H31.401-H31.8,H35.50-H35.54,H35.711-H35.719,H44.421-H44.429  
CPT: 66020,67005-67028,67036-67043,67210,67515,68200,92002-92014,92018-92060,92081-92100,92134,92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- CPT 67027 (Implantation of intravitreal drug delivery system) is included on this line for use with medications other than intraocular steroid implants.
- Line: 384**  
Condition: DENTAL CONDITIONS (E.G., PULPAL PATHOLOGY, PERMANENT ANTERIOR TOOTH)  
Treatment: BASIC ENDODONTICS (I.E., ROOT CANAL THERAPY)  
HCPCS: D3310,D3332



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**Line: 385**  
Condition: SUPERFICIAL INJURIES WITH INFECTION (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: L08.89-L08.9,T79.8XXA-T79.8XXD  
CPT: 10120-10160,11000,11001,12001-12014,28190,29515,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 386**  
Condition: PITUITARY DWARFISM (See Guideline Notes 64,65,74)  
Treatment: MEDICAL THERAPY  
ICD-10: E23.0,Q77.0-Q77.1,Q77.4-Q77.5,Q77.7-Q77.8  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9558

**Line: 387**  
Condition: ANOGENITAL VIRAL WARTS (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: A63.0  
CPT: 11420-11426,17000-17004,46900-46924,54050-54065,56501,56515,57061,57065,57150,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 388**  
Condition: SEPARATION ANXIETY DISORDER (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F93.0  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0019,H0023,H0032-H0038,H0045,H2010,H2012-H2014,H2021,H2022,H2027,H2032,H2033,S9484,T1005

**Line: 389**  
Condition: ACUTE OTITIS MEDIA (See Guideline Notes 29,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: H65.00-H65.07,H65.111-H65.199,H66.001-H66.019,H66.40-H66.93,H67.1-H67.9,H68.011-H68.019,H69.90-H69.93,H73.001-H73.099,H73.20-H73.23,T70.0XXA-T70.0XXD  
CPT: 69209,69210,69420,69421,69433,69436,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 390**  
Condition: INTESTINAL DISACCHARIDASE AND OTHER DEFICIENCIES (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: E72.52-E72.53,E74.10,E74.31-E74.39  
CPT: 93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 391**  
Condition: PANIC DISORDER; AGORAPHOBIA (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F40.00-F40.02,F41.0  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99324-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

- Line: 392**  
Condition: CROUP SYNDROME, EPIGLOTTITIS, ACUTE LARYNGOTRACHEITIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY, INTUBATION, TRACHEOTOMY  
ICD-10: J04.10-J04.2,J04.31,J05.0,J05.10-J05.11  
CPT: 31600,31601,31820-31830,93792,93793,94640,94664,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 393**  
Condition: STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN (See Coding Specification Below) (See Guideline Notes 64,65,134)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: E70.310-E70.329,H02.521-H02.529,H04.531-H04.539,H49.13,H50.00,H50.011-H50.89,H51.0,H51.11-H51.8,H53.2,H53.30-H53.34,H55.00-H55.01,H55.03,H55.09,Q10.0-Q10.7,Q11.0-Q11.3,Q13.0,Q13.2,Q13.4-Q13.5,Q13.89-Q13.9,Q14.0-Q14.9,Q15.8  
CPT: 65778-65782,66820-66986,67311-67345,67901-67909,68135,68320-68328,68335,68340,68371,68810-68840,92002-92014,92018-92065,92081-92136,92225,92226,92230-92310,92314,92325-92342,92370,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514  
  
Chemodenervation with botulinum toxin injection (CPT 67345) is included on this line for the treatment of strabismus due to other neurological disorders (ICD-10 H50.89). CPT 92065 is included on Line 393 only for pairing with ICD-10 H50.31 intermittent monocular esotropia), H50.32 (Intermittent alternating esotropia), H50.33 (Intermittent monocular exotropia), and H50.34 (Intermittent alternating exotropia).
- Line: 394**  
Condition: ANAL FISTULA (See Guideline Notes 64,65)  
Treatment: SPHINCTEROTOMY, FISSURECTOMY, FISTULECTOMY, MEDICAL THERAPY  
ICD-10: K60.3-K60.5  
CPT: 45905,45910,46020,46030,46080,46200,46270-46288,46700,46706,46707,46940,46942,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 395**  
Condition: ENDOMETRIOSIS AND ADENOMYOSIS (See Guideline Notes 39,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: N80.0-N80.9  
CPT: 49203-49205,49322,58145-58150,58260-58263,58290-58292,58550-58554,58570-58573,58660-58662,58740,58940,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9560
- Line: 396**  
Condition: ACUTE MYELOID LEUKEMIA (See Guideline Notes 7,11,12,16)  
Treatment: BONE MARROW TRANSPLANT AND MEDICAL THERAPY, WHICH INCLUDES CHEMOTHERAPY, RADIATION AND RADIONUCLIDE THERAPY  
ICD-10: C92.00-C92.02,C92.50-C92.A2,C93.00-C93.02,C94.00-C94.6,D61.810,G89.3,Z45.49,Z48.290,Z51.0,Z51.12,Z52.000-Z52.098,Z52.3  
CPT: 32553,36680,38100,38120,38204-38215,38230-38243,38760,49411,77014,77261-77290,77295,77300,77306,77307,77321-77370,77385-77387,77401-77427,77469,77520-77525,81246,86828-86835,93792,93793,95990,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S2142,S2150,S9537



**PRIORITIZED LIST OF HEALTH SERVICES  
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- Line: 397**  
Condition: MYELOID DISORDERS (See Guideline Notes 7,11,12,16)  
Treatment: MEDICAL THERAPY, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C92.00-C92.02,C92.50-C92.92,C93.00-C93.02,C93.90-C93.92,C94.00-C94.6,C95.00-C95.02,D45,D61.810,G89.3,Z45.49,Z51.0,Z51.12  
CPT: 32553,38100,38120,38760,49411,77014,77261-77290,77295,77300,77306,77307,77321-77370,77385-77387,77401-77427,77469,77520-77525,81246,93792,93793,95990,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99195,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537
- Line: 398**  
Condition: INFLUENZA (See Guideline Notes 64,65,87)  
Treatment: MEDICAL THERAPY  
ICD-10: J09.X1-J09.X9,J10.00-J10.89,J11.00-J11.89  
CPT: 93792,93793,94640,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 399**  
Condition: CHRONIC MYELOID LEUKEMIA  
Treatment: BONE MARROW TRANSPLANT  
ICD-10: C92.10-C92.22,C93.10-C93.12,C93.90-C93.92,D61.810,T86.5,Z48.290,Z52.000-Z52.098,Z52.3  
CPT: 36680,38204-38215,38230-38243,86825-86835,90284,93792,93793,96377,96405,96406,96420-96440,96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S2142,S2150,S9537
- Line: 400**  
Condition: BENIGN CONDITIONS OF BONE AND JOINTS AT HIGH RISK FOR COMPLICATIONS (See Guideline Notes 6,7,11,64,65,94,100,137)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: D16.00-D16.9,D17.79,D18.09,D48.1,K09.0-K09.1,M12.20,M12.211-M12.29,M27.1,M27.40-M27.49,M67.80,M67.811-M67.89,M85.40,M85.411-M85.69,Q67.6,Q79.8,Z51.0,Z51.12  
CPT: 11400-11446,12051,12052,13131,17106-17111,20150,20550,20551,20600-20611,20615,20930-20938,20955-20973,21011-21014,21025-21032,21040,21046-21049,21181,21552-21556,21600,21740-21743,21930-21936,22532-22819,22853,22854,22859,23071-23076,23101-23106,23140-23156,23200,24071-24079,24102-24126,24420,24498,25000,25071,25073,25105,25110-25136,25170-25240,25295-25301,25320,25335,25337,25390-25393,25441-25447,25450-25492,25810-25830,26100-26116,26130,26200-26215,26250-26262,26449,27025,27043-27049,27054,27059,27065-27078,27187,27327,27328,27334-27339,27355-27358,27365,27465-27468,27495,27625-27638,27645-27647,27656,27745,28039-28045,28070,28072,28100-28108,28122,28124,28171-28175,28820,28825,29820,29821,29835,29836,29844,29845,29863,29875,29876,29895,29905,32553,36680,49411,63081-63103,64774,64792,77014,77261-77295,77300-77307,77331-77338,77385-77387,77401-77427,77469,77470,79005-79445,93792,93793,96377,96405,96406,96420-96440,96450,96542,96549,96570,96571,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017
- Line: 401**  
Condition: CONDITIONS OF THE BACK AND SPINE (See Guideline Notes 56,60,64,65,92,160)  
Treatment: RISK ASSESSMENT, PHYSICAL MODALITIES, COGNITIVE BEHAVIORAL THERAPY, MEDICAL THERAPY  
ICD-10: F45.42,G83.4,G95.0,M24.08,M25.78,M40.00-M40.15,M40.202-M40.57,M42.00-M42.09,M42.11-M42.9,M43.00-M43.4,M43.5X2-M43.5X9,M43.8X1-M43.9,M45.0-M45.9,M46.1,M46.40-M46.99,M47.011-M47.9,M48.00-M48.05,M48.061-M48.38,M48.8X1-M48.9,M49.80-M49.89,M50.00-M50.01,M50.020-M50.93,M51.04-M51.9,M53.2X1-M53.9,M54.00-M54.9,M62.830,M96.1-M96.4,M99.00-M99.09,M99.20-M99.79,M99.81-M99.84,Q06.0-Q06.3,Q06.8-Q06.9,Q68.0,Q76.0-Q76.2,Q76.411-Q76.49,S13.0XXA-S13.0XXD,S13.4XXA-S13.4XXD,S13.8XXA-S13.8XXD,S13.9XXA-S13.9XXD,S16.1XXA-S16.1XXD,S23.0XXA-S23.0XXD,S23.100A-S23.100D,S23.101A-S23.101D,S23.110A-S23.110D,S23.111A-S23.111D,S23.120A-S23.120D,S23.121A-S23.121D,S23.122A-S23.122D,S23.123A-S23.123D,S23.130A-S23.130D,S23.131A-S23.131D,S23.132A-S23.132D,S23.133A-S23.133D,S23.140A-S23.140D,S23.141A-S23.141D,S23.142A-S23.142D,S23.143A-S23.143D,S23.150A-S23.150D,S23.151A-S23.151D,S23.152A-S23.152D,S23.153A-S23.153D,S23.160A-S23.160D,S23.161A-S23.161D,S23.162A-S23.162D,S23.163A-S23.163D,S23.170A-S23.170D,S23.171A-S23.171D,S23.3XXA-S23.3XXD,S23.8XXA-S23.8XXD,S23.9XXA-S23.9XXD,S33.0XXA-S33.0XXD,S33.100A-S33.100D,S33.101A-S33.101D,S33.110A-S33.110D,S33.111A-S33.111D,S33.120A-S33.120D,S33.121A-S33.121D,S33.130A-S33.130D,S33.131A-S33.131D,S33.140A-S33.140D,S33.141A-S33.141D,S33.5XXA-S33.5XXD,S33.8XXA-



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S33.8XXD,S33.9XXA-S33.9XXD,S34.3XXA-S34.3XXD,S39.092A-S39.092D,S39.82XA-S39.82XD,S39.92XA-S39.92XD  
CPT: 90785,90832-90840,90853,93792,93793,96150-96155,97110-97124,97140-97168,97530,97535,97810-98942,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99304-99337,99340-99404,99408-99449,99487-99490,99495,99496,99605-99607  
HCPCS: G0157-G0160,G0248-G0250,G0396,G0397,G0425-G0427,G0463-G0467,G0469,G0470,G0490,G0511,G0513,G0514,S9451

**Line: 402**  
Condition: LYMPHADENITIS (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: I88.0-I88.8,L04.0-L04.9  
CPT: 10030,10060,10061,38300-38308,38542,49405-49407,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 403**  
Condition: UTERINE LEIOMYOMA AND POLYPS (See Guideline Notes 40,64,65)  
Treatment: SURGICAL TREATMENT  
ICD-10: D25.0-D25.9,D26.0-D26.9,D39.0,N84.0,N84.8-N84.9,N85.2-N85.3  
CPT: 37243,58120-58180,58260-58263,58290-58292,58541-58554,58559,58561,58570-58573,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9560

**Line: 404**  
Condition: APHAKIA AND OTHER DISORDERS OF LENS (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL THERAPY  
ICD-10: H27.00-H27.10,H27.111-H27.8  
CPT: 65750,65765,65767,66825,66985-66990,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,92311,92312,92352,92353,92358,92371,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 405**  
Condition: BILATERAL ANOMALIES OF EXTERNAL EAR WITH IMPAIRMENT OF HEARING (See Guideline Notes 64,65)  
Treatment: RECONSTRUCT OF EAR CANAL  
ICD-10: H61.301-H61.399,Q16.0-Q16.1,Q16.3-Q16.9,Z01.12  
CPT: 69310,69320,69631-69637,92562-92565,92571-92577,92590,92591,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 406**  
Condition: DISSOCIATIVE DISORDERS (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F44.0-F44.2,F44.81-F44.89,F48.1  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99324-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005

**Line: 407**  
Condition: EPIDERMOLYSIS BULLOSA (See Guideline Notes 6,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: Q81.0-Q81.9  
CPT: 11000,11001,93792,93793,96150-96155,96900,96902,96910-96913,97012,97110-97124,97140-97168,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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**Line: 408**  
Condition: DELIRIUM DUE TO MEDICAL CAUSES (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: F05  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 409**  
Condition: MIGRAINE HEADACHES (See Guideline Notes 42,64,65,92)  
Treatment: MEDICAL THERAPY  
ICD-10: G43.001-G43.719,G43.B0-G43.C1,G43.801-G43.919,G44.001-G44.1  
CPT: 64615,92002-92014,92081-92083,93792,93793,96150-96155,97810-97814,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 410**  
Condition: DENTAL CONDITIONS (E.G., PULPAL PATHOLOGY, PERMANENT BICUSPID/PREMOLAR TOOTH)  
Treatment: BASIC ENDODONTICS (I.E., ROOT CANAL THERAPY)  
HCPCS: D3320,D3332

**Line: 411**  
Condition: SCHIZOTYPAL PERSONALITY DISORDERS (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F21  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99324-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0018,H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005

**Line: 412**  
Condition: BALANOPOSTHITIS AND OTHER DISORDERS OF PENIS (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: N47.2,N47.6,N48.1,N48.5  
CPT: 53431,54000-54015,54110-54112,54200,54205,54230,54231,54240,54250,54450,74445,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 413**  
Condition: OVERANXIOUS DISORDER; GENERALIZED ANXIETY DISORDER; ANXIETY DISORDER, UNSPECIFIED (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F41.1-F41.9  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0019,H0023,H0032-H0034,H0036-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,H2033,S5151,S9125,S9484,T1005

**Line: 414**  
Condition: TRANSIENT CEREBRAL ISCHEMIA; OCCLUSION/STENOSIS OF PRECEREBRAL ARTERIES WITHOUT OCCLUSION (See Guideline Notes 64,65,119,125)  
Treatment: MEDICAL THERAPY; THROMBOENDARTERECTOMY  
ICD-10: G45.0-G45.3,G45.8-G45.9,G46.0-G46.2,H34.00-H34.03,H93.011-H93.019,I65.01-I65.9,I66.01-I66.9,I77.71,I77.74-I77.75,Z86.73  
CPT: 34001,35301,35390,35606,37215-37218,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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- Line: 415**  
Condition: PERIPHERAL NERVE ENTRAPMENT; PALMAR FASCIAL FIBROMATOSIS (See Guideline Notes 6,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: G56.00-G56.03,G56.20-G56.23,G57.30-G57.53,M53.1,M72.0  
CPT: 20526,25109,25111,25118,25447,26035,26045,26060,26121-26180,26320,26440-26498,28035,29105,29515,29848,64702,64704,64718-64727,64774-64783,64788-64792,64856,64857,64872-64907,93792,93793,97012,97018,97110-97124,97140-97168,97530,98925-98942,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 416**  
Condition: MENIERE'S DISEASE (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: H81.01-H81.09  
CPT: 69666,69667,69801-69806,69915,69950,92531-92548,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 417**  
Condition: DISORDERS OF SHOULDER, INCLUDING SPRAINS/STRAINS GRADE 4 THROUGH 6 (See Guideline Notes 6,64,65,97)  
Treatment: REPAIR/RECONSTRUCTION, MEDICAL THERAPY  
ICD-10: M24.011-M24.019,M24.111-M24.119,M24.311-M24.319,M24.611-M24.619,M24.811-M24.819,M25.211-M25.219,M25.311-M25.319,M25.711-M25.719,M66.211-M66.219,M66.811-M66.819,M75.00-M75.02,M75.100-M75.122,M75.30-M75.92,S43.401A-S43.401D,S43.402A-S43.402D,S43.409A-S43.409D,S43.411A-S43.411D,S43.412A-S43.412D,S43.419A-S43.419D,S43.421A-S43.421D,S43.422A-S43.422D,S43.429A-S43.429D,S43.431A-S43.431D,S43.432A-S43.432D,S43.439A-S43.439D,S43.491A-S43.491D,S43.492A-S43.492D,S43.499A-S43.499D,S43.50XA-S43.50XD,S43.51XA-S43.51XD,S43.52XA-S43.52XD,S43.60XA-S43.60XD,S43.61XA-S43.61XD,S43.62XA-S43.62XD,S43.80XA-S43.80XD,S43.81XA-S43.81XD,S43.82XA-S43.82XD,S43.90XA-S43.90XD,S43.91XA-S43.91XD,S43.92XA-S43.92XD,S46.011A-S46.011D,S46.012A-S46.012D,S46.019A-S46.019D,S46.111A-S46.111D,S46.112A-S46.112D,S46.119A-S46.119D,S46.211A-S46.211D,S46.212A-S46.212D,S46.219A-S46.219D,S46.311A-S46.311D,S46.312A-S46.312D,S46.319A-S46.319D,S46.811A-S46.811D,S46.812A-S46.812D,S46.819A-S46.819D,S46.911A-S46.911D,S46.912A-S46.912D,S46.919A-S46.919D,Z47.31  
CPT: 20550,20610,20611,20615,23000,23020,23105-23130,23190,23195,23334,23335,23395,23410-23460,23490,23491,23650-23700,29807-29828,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98925-98942,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 418**  
Condition: CHRONIC LEUKEMIAS WITH POOR PROGNOSIS (See Guideline Notes 7,11,12)  
Treatment: MEDICAL THERAPY, WHICH INCLUDES CHEMOTHERAPY, RADIATION AND RADIONUCLEIDE THERAPY  
ICD-10: C91.10-C91.92,C93.Z0-C93.Z2,C94.80-C94.82,C95.10-C95.92,D61.810,G89.3,Z51.0,Z51.12  
CPT: 32553,49411,77014,77261-77290,77295,77300,77306,77307,77321-77370,77385-77387,77401-77417,77424-77427,77469,79101,90284,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99195,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537
- Line: 419**  
Condition: OPPOSITIONAL DEFIANT DISORDER (See Guideline Notes 64,65,152)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F91.3,F91.9  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0034,H0036-H0039,H0045,H2010,H2012,H2014,H2021,H2022,H2027,H2032,H2033,S5151,S9125,S9480,S9484,T1005



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<b>Line:</b>	<b>420</b>
Condition:	MENSTRUAL BLEEDING DISORDERS (See Guideline Notes 44,64,65,88)
Treatment:	MEDICAL AND SURGICAL TREATMENT
ICD-10:	N85.01,N85.5,N92.0-N92.6,Q51.5
CPT:	57800,58120,58150,58180,58260,58262,58290,58291,58300,58301,58353,58356,58541-58544,58550-58554,58561-58563,58570-58573,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>421</b>
Condition:	LYMPHEDEMA (See Guideline Notes 6,43,64,65,149)
Treatment:	MEDICAL THERAPY, OTHER OPERATION ON LYMPH CHANNEL
ICD-10:	I89.0,I89.8-I89.9,I97.2,Q82.0
CPT:	29581,29584,38300-38382,38542-38555,38700-38745,38747,38760,49062,49185,49323,49423,93792,93793,97016,97110,97124,97140,97161-97168,97530,97760,97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>422</b>
Condition:	COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT (See Coding Specification Below) (See Guideline Notes 6,62,64,65,149,157)
Treatment:	MEDICAL AND SURGICAL TREATMENT
ICD-10:	D78.31-D78.89,E36.8,E89.810-E89.89,G89.22,G96.11,G97.1,G97.41,H59.011-H59.099,H59.811-H59.89,H74.8X1-H74.8X9,H95.811-H95.89,I97.3,J95.00,K91.61-K91.62,K91.840-K91.858,K94.00,K94.03-K94.10,K94.13-K94.20,K94.23-K94.30,K94.32-K94.39,K95.09-K95.89,L27.0,L58.0,L64.0,L65.8,L76.01-L76.02,L76.21-L76.82,M96.810-M96.811,M96.830-M96.89,N98.1-N98.9,N99.110-N99.114,N99.61-N99.62,N99.820-N99.821,N99.840-N99.843,O89.4,T66.XXXA-T66.XXXD,T80.1XXA-T80.1XXD,T80.30XA-T80.30XD,T80.310A-T80.310D,T80.311A-T80.311D,T80.319A-T80.319D,T80.39XA-T80.39XD,T80.40XA-T80.40XD,T80.410A-T80.410D,T80.411A-T80.411D,T80.419A-T80.419D,T80.49XA-T80.49XD,T80.A0XA-T80.A0XD,T80.A10A-T80.A10D,T80.A11A-T80.A11D,T80.A19A-T80.A19D,T80.A9XA-T80.A9XD,T80.61XA-T80.61XD,T80.62XA-T80.62XD,T80.69XA-T80.69XD,T81.500A-T81.500D,T81.501A-T81.501D,T81.502A-T81.502D,T81.503A-T81.503D,T81.504A-T81.504D,T81.505A-T81.505D,T81.506A-T81.506D,T81.507A-T81.507D,T81.508A-T81.508D,T81.509A-T81.509D,T81.510A-T81.510D,T81.511A-T81.511D,T81.512A-T81.512D,T81.513A-T81.513D,T81.514A-T81.514D,T81.515A-T81.515D,T81.516A-T81.516D,T81.517A-T81.517D,T81.518A-T81.518D,T81.519A-T81.519D,T81.527A-T81.527D,T81.528A-T81.528D,T81.529A-T81.529D,T81.530A-T81.530D,T81.531A-T81.531D,T81.532A-T81.532D,T81.533A-T81.533D,T81.534A-T81.534D,T81.535A-T81.535D,T81.536A-T81.536D,T81.537A-T81.537D,T81.538A-T81.538D,T81.539A-T81.539D,T81.590A-T81.590D,T81.591A-T81.591D,T81.592A-T81.592D,T81.593A-T81.593D,T81.594A-T81.594D,T81.595A-T81.595D,T81.596A-T81.596D,T81.597A-T81.597D,T81.598A-T81.598D,T81.599A-T81.599D,T81.60XA-T81.60XD,T81.61XA-T81.61XD,T81.69XA-T81.69XD,T81.89XA-T81.89XD,T83.018A-T83.018D,T83.021A-T83.021D,T83.028A-T83.028D,T83.031A-T83.031D,T83.038A-T83.038D,T83.091A-T83.091D,T83.098A-T83.098D,T83.31XA-T83.31XD,T83.32XA-T83.32XD,T83.39XA-T83.39XD,T83.411A-T83.411D,T83.421A-T83.421D,T83.491A-T83.491D,T83.711A-T83.711D,T83.712A-T83.712D,T83.713A-T83.713D,T83.714A-T83.714D,T83.718A-T83.718D,T83.719A-T83.719D,T83.721A-T83.721D,T83.722A-T83.722D,T83.723A-T83.723D,T83.724A-T83.724D,T83.728A-T83.728D,T83.729A-T83.729D,T83.79XA-T83.79XD,T85.21XA-T85.21XD,T85.22XA-T85.22XD,T85.29XA-T85.29XD,T85.310A-T85.310D,T85.311A-T85.311D,T85.318A-T85.318D,T85.320A-T85.320D,T85.321A-T85.321D,T85.328A-T85.328D,T85.390A-T85.390D,T85.391A-T85.391D,T85.398A-T85.398D,T85.41XA-T85.41XD,T85.42XA-T85.42XD,T85.43XA-T85.43XD,T85.44XA-T85.44XD,T85.49XA-T85.49XD,T85.510A-T85.510D,T85.511A-T85.511D,T85.518A-T85.518D,T85.520A-T85.520D,T85.521A-T85.521D,T85.528A-T85.528D,T85.590A-T85.590D,T85.591A-T85.591D,T85.598A-T85.598D,T85.610A-T85.610D,T85.612A-T85.612D,T85.613A-T85.613D,T85.614A-T85.614D,T85.618A-T85.618D,T85.620A-T85.620D,T85.622A-T85.622D,T85.623A-T85.623D,T85.624A-T85.624D,T85.628A-T85.628D,T85.630A-T85.630D,T85.633A-T85.633D,T85.638A-T85.638D,T85.690A-T85.690D,T85.692A-T85.692D,T85.693A-T85.693D,T85.694A-T85.694D,T85.698A-T85.698D,T85.840A-T85.840D,T85.848A-T85.848D,T86.820-T86.829,T87.30-T87.34,T87.81-T87.9,T88.52XA-T88.52XD,T88.53XA-T88.53XD,T88.59XA-T88.59XD,T88.8XXA-T88.8XXD,Z45.42,Z45.82,Z47.32-Z47.33
CPT:	10030,10140,10160,11042-11047,11976,11982,11983,13160,15002-15005,19328,19330,19371,19380,20661,20680,20694,21120,21501,22849-22852,22855,24160,24164,25250,25251,25449,25909,26320,26990,27090,27091,27132-27138,27265,27266,27301,27486-27488,27570,27603,27704,27884,27886,29584,31613,31614,31630,31631,31636-31638,31641,31645,31750-31781,31800-31830,33922,35875,35876,35901-35905,36860,36861,37224,37228,43285,43771-43774,43848,43870,44227,44312,44314,44340-44346,44620-44626,47536,47537,49185,49422,49429,53442,53446-53449,57295,57296,58301,58562,62100,62273,63661-63664,63688,63707,63709,64595,64788,65150-65175,65920,66825,66985,66986,67036,67121,67560,69424,69711,75984,92002-92014,92507,92508,92521-92526,92607-92609,92633,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97605-97608,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	A9282,G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9152
ICD-10-CM codes L58.0, L64.0 and L65.8 are only included on this line for pairing with HCPC A9282.	



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

- Line: 423**  
Condition: ADRENOGENITAL DISORDERS (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: E25.0-E25.9, Q56.0-Q56.4  
CPT: 50700, 54690, 56800-56810, 57335, 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514
- Line: 424**  
Condition: SEVERE INFLAMMATORY SKIN DISEASE (See Coding Specification Below) (See Guideline Note 21)  
Treatment: MEDICAL THERAPY  
ICD-10: H01.121-H01.129, L20.82-L20.9, L40.0-L40.4, L40.8-L40.9, L41.0-L41.9, L43.0-L43.9, L44.0, L93.0, Q82.8  
CPT: 93792, 93793, 96150-96155, 96900, 96902, 96910-96922, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514  
  
ICD-10-CM Q82.8 is included on this line only for Darier disease.
- Line: 425**  
Condition: ACUTE PERIPHERAL MOTOR AND DIGITAL NERVE INJURY (See Guideline Note 133)  
Treatment: SURGICAL THERAPY  
ICD-10: G57.20-G57.23, S74.00XA-S74.00XD, S74.01XA-S74.01XD, S74.02XA-S74.02XD, S74.10XA-S74.10XD, S74.11XA-S74.11XD, S74.12XA-S74.12XD  
CPT: 20550, 20551, 21032, 24105, 24357-24359, 25109, 25447, 26035, 26060, 26121-26180, 26320, 26440-26556, 26565-26596, 26820-26863, 27060, 27097, 27100-27122, 27140-27165, 27306, 27307, 27448-27455, 27466, 27468, 27475-27485, 27715, 27730-27742, 28119, 64702, 64704, 64718-64727, 64774, 64856, 64857, 64872-64907, 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0157-G0161, G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514
- Line: 426**  
Condition: NON-MALIGNANT OTITIS EXTERNA (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: B37.84, H60.311-H60.399, H62.40-H62.43  
CPT: 69000, 69020, 69209, 69210, 92633, 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99201-99215, 99281-99285, 99341-99378, 99381-99404, 99408-99449, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0463-G0467, G0490, G0511, G0513, G0514
- Line: 427**  
Condition: VAGINITIS AND CERVICITIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A56.02, A59.00-A59.9, B37.3, N72, N76.0-N76.3, N77.1, N89.8  
CPT: 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99201-99215, 99281-99285, 99341-99378, 99381-99404, 99408-99449, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0463-G0467, G0490, G0511, G0513, G0514
- Line: 428**  
Condition: NONINFLAMMATORY DISORDERS AND BENIGN NEOPLASMS OF OVARY, FALLOPIAN TUBES AND UTERUS; OVARIAN CYSTS; GONADAL DYSGENESIS (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: D27.0-D27.9, D28.2, N83.00-N83.12, N83.201-N83.299, N83.40-N83.42, N83.7, Q50.01-Q50.39  
CPT: 49322, 58559, 58561, 58562, 58660-58662, 58700-58740, 58800, 58805, 58900-58943, 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514
- Line: 429**  
Condition: URETHRAL FISTULA (See Guideline Notes 64,65)  
Treatment: EXCISION, MEDICAL THERAPY  
ICD-10: N36.0-N36.1, N36.5  
CPT: 45820, 53230-53250, 53520, 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

**Line: 430**  
Condition: INTERNAL DERANGEMENT OF KNEE AND LIGAMENTOUS DISRUPTIONS OF THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT (See Guideline Notes 6,64,65,98,104)  
Treatment: REPAIR, MEDICAL THERAPY  
ICD-10: M22.2X1-M22.3X9,M22.8X1-M22.8X9,M23.011-M23.205,M23.211-M23.305,M23.311-M23.8X9,M24.661-M24.669,M66.261-M66.269,S83.200A-S83.200D,S83.201A-S83.201D,S83.202A-S83.202D,S83.203A-S83.203D,S83.204A-S83.204D,S83.205A-S83.205D,S83.206A-S83.206D,S83.207A-S83.207D,S83.209A-S83.209D,S83.211A-S83.211D,S83.212A-S83.212D,S83.219A-S83.219D,S83.221A-S83.221D,S83.222A-S83.222D,S83.229A-S83.229D,S83.231A-S83.231D,S83.232A-S83.232D,S83.239A-S83.239D,S83.241A-S83.241D,S83.242A-S83.242D,S83.249A-S83.249D,S83.251A-S83.251D,S83.252A-S83.252D,S83.259A-S83.259D,S83.261A-S83.261D,S83.262A-S83.262D,S83.269A-S83.269D,S83.271A-S83.271D,S83.272A-S83.272D,S83.279A-S83.279D,S83.281A-S83.281D,S83.282A-S83.282D,S83.289A-S83.289D,S83.30XA-S83.30XD,S83.31XA-S83.31XD,S83.32XA-S83.32XD,S83.401A-S83.401D,S83.402A-S83.402D,S83.409A-S83.409D,S83.411A-S83.411D,S83.412A-S83.412D,S83.419A-S83.419D,S83.421A-S83.421D,S83.422A-S83.422D,S83.429A-S83.429D,S83.501A-S83.501D,S83.502A-S83.502D,S83.509A-S83.509D,S83.511A-S83.511D,S83.512A-S83.512D,S83.519A-S83.519D,S83.521A-S83.521D,S83.522A-S83.522D,S83.529A-S83.529D,S83.60XA-S83.60XD,S83.61XA-S83.61XD,S83.62XA-S83.62XD,S83.8X1A-S83.8X1D,S83.8X2A-S83.8X2D,S83.8X9A-S83.8X9D,S83.90XA-S83.90XD,S83.91XA-S83.91XD,S83.92XA-S83.92XD,S86.111A-S86.111D,S86.112A-S86.112D,S86.119A-S86.119D,S86.211A-S86.211D,S86.212A-S86.212D,S86.219A-S86.219D,S86.311A-S86.311D,S86.312A-S86.312D,S86.319A-S86.319D,S86.811A-S86.811D,S86.812A-S86.812D,S86.819A-S86.819D,S86.911A-S86.911D,S86.912A-S86.912D,S86.919A-S86.919D  
CPT: 20610,20611,27332-27335,27340,27350,27380,27381,27403-27416,27420-27430,27570,29345-29445,29505,29530,29705,29871-29889,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 431**  
Condition: PERSISTENT DEPRESSIVE DISORDER (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F34.1  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0023,H0032-H0034,H0036-H0039,H0045,H2010,H2012,H2014,H2021-H2023,H2027,H2032,H2033,S9480,S9484

**Line: 432**  
Condition: HYPOSPADIAS AND EPISPADIAS (See Guideline Notes 64,65,72,73)  
Treatment: REPAIR  
ICD-10: Q54.0-Q54.8,Q55.5,Q55.61-Q55.69,Q64.0,S39.840A-S39.840D  
CPT: 51715,53431,54230,54231,54240-54390,54420,54430,54440,55175,55180,74445,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 433**  
Condition: CANCER OF GALLBLADDER AND OTHER BILIARY (See Guideline Notes 7,11,12,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: C23,C24.0-C24.9,D01.5,D61.810,G89.3,Z51.0,Z51.11-Z51.12  
CPT: 32553,43260-43265,43273-43278,47533-47540,47542,47562-47570,47600-47620,47711,47712,47741,47785,48145-48155,49327,49411,49412,60540,77014,77261-77290,77295,77300,77306-77370,77385-77387,77402-77417,77424-77432,77469,77470,79005-79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

**Line: 434**  
Condition: PRECANCEROUS VULVAR CONDITIONS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: L90.0,N90.0-N90.1,N90.4-N90.5  
CPT: 56501,56515,56620,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

**Line: 435**  
Condition: RECURRENT EROSION OF THE CORNEA (See Guideline Notes 64,65)  
Treatment: ANTERIAL STROMAL PUNCTURE, REMOVAL OF CORNEAL EPITHELIUM; WITH OR WITHOUT CHEMOCAUTERIZATION  
ICD-10: H18.831-H18.839  
CPT: 65430,65435,65600,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 436**  
Condition: STEREOTYPED MOVEMENT DISORDER WITH SELF-INJURIOUS BEHAVIOR DUE TO NEURODEVELOPMENTAL DISORDER (See Guideline Notes 64,65,126)  
Treatment: CONSULTATION/MEDICATION MANAGEMENT/LIMITED BEHAVIORAL MODIFICATION  
ICD-10: F98.4  
CPT: 0359T-0374T,90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99281-99285,99304-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017,H0019,H0023,H0032-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9480,S9484,T1005

**Line: 437**  
Condition: FOREIGN BODY IN UTERUS, VULVA AND VAGINA (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: T19.2XXA-T19.2XXD,T19.3XXA-T19.3XXD  
CPT: 57415,58120,58562,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 438**  
Condition: RESIDUAL FOREIGN BODY IN SOFT TISSUE  
Treatment: REMOVAL  
ICD-10: H02.811-H02.819,M79.5,Z18.01-Z18.89  
CPT: 10120,10121,20520,20525,23330,23333,24200,24201,25248,27086,27087,27372,28190-28193,40804,41805,55120,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 439**  
Condition: VENOUS TRIBUTARY (BRANCH) OCCLUSION; CENTRAL RETINAL VEIN OCCLUSION (See Guideline Notes 64,65,116)  
Treatment: SURGICAL TREATMENT INCLUDING LASER SURGERY, MEDICAL THERAPY INCLUDING INJECTION  
ICD-10: H34.8110-H34.8192,H34.8310-H34.9  
CPT: 67028,67228,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 440**  
Condition: TRIGEMINAL AND OTHER NERVE DISORDERS (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES RADIATION THERAPY  
ICD-10: G50.0-G50.9,G52.0-G52.9,G53,Z45.42,Z51.0  
CPT: 32553,49411,61450,61458,61790-61800,64568-64570,64600-64610,64716,77014,77261-77295,77300,77301,77332-77372,77402,77417-77432,77469,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 441**  
Condition: MALUNION AND NONUNION OF FRACTURE (See Guideline Notes 6,64,65)  
Treatment: SURGICAL TREATMENT  
ICD-10: M80.00XK-M80.00XP,M80.011K-M80.011P,M80.012K-M80.012P,M80.019K-M80.019P,M80.021K-M80.021P,M80.022K-M80.022P,M80.029K-M80.029P,M80.031K-M80.031P,M80.032K-M80.032P,M80.039K-M80.039P,M80.041K-M80.041P,M80.042K-M80.042P,M80.049K-M80.049P,M80.051K-M80.051P,M80.052K-M80.052P,M80.059K-M80.059P,M80.061K-M80.061P,M80.062K-M80.062P,M80.069K-M80.069P,M80.071K-M80.071P,M80.072K-M80.072P,M80.079K-M80.079P,M80.08XK-M80.08XP,M80.80XK-M80.80XP,M80.811K-M80.811P,M80.812K-M80.812P,M80.819K-M80.819P,M80.821K-M80.821P,M80.822K-M80.822P,M80.829K-M80.829P,M80.831K-M80.831P,M80.832K-M80.832P,M80.839K-M80.839P,M80.841K-M80.841P,M80.842K-M80.842P,



PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

M80.849K-M80.849P,M80.851K-M80.851P,M80.852K-M80.852P,M80.859K-M80.859P,M80.861K-M80.861P,  
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PRIORITIZED LIST OF HEALTH SERVICES  
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S42.116K-S42.116P,S42.121K-S42.121P,S42.122K-S42.122P,S42.123K-S42.123P,S42.124K-S42.124P,  
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PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

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PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

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PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

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S99.212K-S99.212P,S99.219K-S99.219P,S99.221K-S99.221P,S99.222K-S99.222P,S99.229K-S99.229P,  
S99.231K-S99.231P,S99.232K-S99.232P,S99.239K-S99.239P,S99.241K-S99.241P,S99.242K-S99.242P,  
S99.249K-S99.249P,S99.291K-S99.291P,S99.292K-S99.292P,S99.299K-S99.299P,Z47.1



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- CPT: 20680-20694,20955-20975,21244,21462,21750,21825,23472-23485,24130,24140,24400,24410,24430,24435,25259,25400-25440,25628,26185,26546,26565,26567,26735,26841,27125-27132,27165,27170,27217,27236,27465-27472,27656,27707,27720-27726,27824-27829,27880-27888,28315-28322,28485,28725,29075,29085,29130,29345,29405,29425,29825,29826,29904-29907,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
- HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 442**  
Condition: DENTAL CONDITIONS (E.G., PULPAL PATHOLOGY, PERMANENT MOLAR TOOTH)  
Treatment: BASIC ENDODONTICS (I.E., ROOT CANAL THERAPY)  
HCPCS: D3330,D3332
- Line: 443**  
Condition: ADJUSTMENT DISORDERS (See Coding Specification Below) (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F43.20-F43.8,F98.9,Z62.810-Z62.898,Z63.4,Z63.8,Z71.89  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0023,H0032-H0038,H0045,H2010,H2012,H2014,H2021-H2023,H2027,H2032,H2033,S5151,S9125,S9484,T1005
- ICD-10-CM codes Z71.89, Other specified counseling, and Z63.4 Disappearance and death of family member are only included in this line when identified as secondary diagnoses with a primary diagnosis of F43.8, Other reactions to severe stress.
- Line: 444**  
Condition: HEARING LOSS - OVER AGE OF FIVE (See Guideline Notes 51,64,65,103,143,154)  
Treatment: MEDICAL THERAPY INCLUDING HEARING AIDS, LIMITED SURGICAL THERAPY  
ICD-10: H72.00-H72.13,H72.2X1-H72.93,H83.3X1-H83.3X9,H90.0,H90.11-H90.8,H90.A11-H90.A32,H91.01-H91.3,H91.8X1-H91.93,H93.091-H93.099,H93.211-H93.249,H93.291-H93.3X9,H94.00-H94.03,S09.20XA-S09.20XD,S09.21XA-S09.21XD,S09.22XA-S09.22XD,Z01.12,Z46.1  
CPT: 42830,42835,69209,69210,69433,69436,69610-69646,69714-69718,92562-92565,92571-92577,92590-92595,92597,92626,92627,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 445**  
Condition: TOURETTE'S DISORDER AND TIC DISORDERS (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F95.0-F95.9  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,96150-96155,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0023,H0032-H0034,H0036-H0038,H2010,H2012-H2014,H2021,H2022,H2027,H2032,S9484
- Line: 446**  
Condition: ATHEROSCLEROSIS, AORTIC AND RENAL (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: I70.0-I70.1  
CPT: 35501-35515,35526,35531,35535-35540,35560,35563,35572,35601-35616,35626-35647,35654,35663,35697,35820,35840,35875,35876,35905,35907,37184-37186,37211,37213,37214,37236,37237,37246,37247,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 447**  
Condition: DEGENERATION OF MACULA AND POSTERIOR POLE (See Guideline Notes 46,64,65)  
Treatment: MEDICAL, SURGICAL AND LASER TREATMENT  
ICD-10: H31.101-H31.20,H31.22-H31.29,H31.301-H31.319,H35.30,H35.3110-H35.389,H35.81,H44.20-H44.23,H44.2A1-H44.2B9,H44.2D1-H44.2E9  
CPT: 66990,67028,67039-67043,67210,67221,67225,67515,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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- Line: 448**  
Condition: REACTIVE ATTACHMENT DISORDER OF INFANCY OR EARLY CHILDHOOD (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F94.1-F94.2  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99324-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0038,H0045,H2010,H2012-H2014,H2021,H2022,H2027,H2032,S5151,S9125,S9484,T1005
- Line: 449**  
Condition: DISORDERS OF REFRACTION AND ACCOMMODATION (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: H52.00-H52.13,H52.201-H52.7,H53.10-H53.11,H53.16-H53.19,H53.50-H53.69,Z46.0  
CPT: 92002-92060,92081-92136,92225,92226,92230-92310,92314,92325-92342,92370,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 450**  
Condition: EXOPHTHALMOS AND CYSTS OF THE EYE AND ORBIT (See Guideline Notes 64,65)  
Treatment: SURGICAL TREATMENT  
ICD-10: H05.20,H05.211-H05.359,H05.811-H05.819,H21.311-H21.329,H21.341-H21.359  
CPT: 67405-67414,67420-67440,67875-67882,68500,68505,68540,68550,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 451**  
Condition: DENTAL CONDITIONS (E.G., MISSING TEETH, PROSTHESIS FAILURE) (See Guideline Note 117)  
Treatment: REMOVABLE PROSTHODONTICS (E.G., FULL AND PARTIAL DENTURES, RELINES)  
ICD-10: K00.0,K08.101-K08.122,K08.124-K08.199,K08.401-K08.499  
HCPCS: D5110-D5212,D5221,D5222,D5511-D5761,D5820,D5821,D7472,D7473,D7970
- Line: 452**  
Condition: RECTAL PROLAPSE (See Guideline Notes 64,65)  
Treatment: SURGICAL TREATMENT  
ICD-10: K62.2-K62.4  
CPT: 44139-44144,44204-44208,44213,44701,45130,45135,45303,45340,45400,45402,45505-45541,45900,46080,46500,46604,46700,46705,46750,46751,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 453**  
Condition: URINARY INCONTINENCE (See Guideline Notes 6,47,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: N36.41-N36.43,N39.3,N39.41-N39.42,N39.46,N39.490-N39.498,R39.81  
CPT: 51840-51845,51990,51992,53446,53448,57160,57220,57260,57267,57280-57289,57423,57425,90911,93792,93793,96150-96155,97110,97140,97161-97164,97530,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 454**  
Condition: DISORDERS OF PLASMA PROTEIN METABOLISM (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: D89.0-D89.2,E88.01-E88.09  
CPT: 36514,36516,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 455**  
Condition: DENTAL CONDITIONS (E.G., PULPAL PATHOLOGY, PERMANENT ANTERIOR TOOTH)  
Treatment: ADVANCED ENDODONTICS (E.G., RETREATMENT OF PREVIOUS ROOT CANAL THERAPY)  
HCPCS: D3331,D3333,D3346,D3410,D3430



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- Line: 456**  
Condition: SIMPLE PHOBIAS AND SOCIAL ANXIETY DISORDER (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F40.10-F40.11,F40.210-F40.9  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0023,H0032-H0038,H2010,H2012,H2014,H2021-H2023,H2027,H2032,H2033,S9484
- Line: 457**  
Condition: ACUTE BRONCHITIS AND BRONCHIOLITIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: B25.0,J20.0-J20.9,J21.0-J21.9,J98.01  
CPT: 31600,31601,31820,31825,93792,93793,94640,94664,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 458**  
Condition: CENTRAL PTERYGIUM AFFECTING VISION (See Guideline Notes 64,65)  
Treatment: EXCISION OR TRANSPOSITION OF PTERYGIUM WITHOUT GRAFT, RADIATION THERAPY  
ICD-10: H11.021-H11.029,Z51.0  
CPT: 32553,49411,65420,65426,77316-77318,77332-77370,77402,77424-77427,77469,77789,79005-79445,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 459**  
Condition: BRANCHIAL CLEFT CYST; THYROGLOSSAL DUCT CYST; CYST OF PHARYNX OR NASOPHARYNX (See Guideline Notes 64,65)  
Treatment: EXCISION, MEDICAL THERAPY  
ICD-10: J39.2,K09.0-K09.1,Q18.0-Q18.2,Q89.2  
CPT: 38550,38555,42808,42810,42815,60000,60280,60281,69145,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 460**  
Condition: OBSESSIVE-COMPULSIVE DISORDERS (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F42.2-F42.9,F45.22,F63.3  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0019,H0023,H0032-H0034,H0036-H0039,H0045,H2010,H2012-H2014,H2021-H2023,H2027,H2032,S9480,S9484,T1005
- Line: 461**  
Condition: OSTEOARTHRITIS AND ALLIED DISORDERS (See Guideline Notes 6,64,65,92,104)  
Treatment: MEDICAL THERAPY, INJECTIONS  
ICD-10: M12.10,M12.111-M12.19,M12.40,M12.411-M12.59,M13.80,M13.811-M13.89,M15.0-M15.9,M16.0,M16.10-M16.9,M17.0,M17.10-M17.9,M18.0,M18.10-M18.9,M19.011-M19.93,M20.20-M20.22,M24.171-M24.176,M24.671-M24.673,M24.871-M24.872,M24.874-M24.875,M25.871-M25.879  
CPT: 11042,11045,20600-20611,25000,29075,93792,93793,96150-96155,97012,97018,97110-97124,97140-97168,97530,97535,97542,97760-97763,97810-98942,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 462**  
Condition: ATELECTASIS (COLLAPSE OF LUNG) (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: J18.2,J98.11-J98.19  
CPT: 31645,31646,93792,93793,94002-94005,94640,94660-94668,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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- Line: 463**  
Condition: CHRONIC SINUSITIS (See Guideline Notes 35,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: J01.01,J01.11,J01.21,J01.31,J01.41,J01.81,J01.91,J32.0-J32.9  
CPT: 30000,30020,30110-30140,30200-30420,30435,30450,30465-30930,31000-31230,31237-31298,42830,42835,61782,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 464**  
Condition: UTERINE PROLAPSE; CYSTOCELE (See Guideline Notes 6,50,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: N81.0,N81.10-N81.9,N99.3  
CPT: 45560,51840,52270,52285,53000,53010,56810,57106,57120,57160,57220-57289,57423,57425,57545,57555,57556,58150,58152,58260-58280,58290-58294,58550-58554,58570-58573,93792,93793,97110,97140,97161-97164,97530,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 465**  
Condition: BRACHIAL PLEXUS LESIONS (See Guideline Notes 6,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: G54.0  
CPT: 21615,21616,21700,21705,93792,93793,97110,97112,97116,97124,97140,97161-97168,98925-98942,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 466**  
Condition: DENTAL CONDITIONS (E.G., CARIES, FRACTURED TOOTH)  
Treatment: ADVANCED RESTORATIVE (I.E., BASIC CROWNS)  
HCPCS: D2710,D2712,D2751,D2752
- Line: 467**  
Condition: GONADAL DYSFUNCTION, MENOPAUSAL MANAGEMENT (See Guideline Notes 64,65,74,88)  
Treatment: OOPHORECTOMY, ORCHIECTOMY, HORMONAL REPLACEMENT FOR PURPOSES OTHER THAN INFERTILITY  
ICD-10: E28.1-E28.2,E28.310-E28.9,E29.0-E29.9,E30.0,E34.50-E34.52,E89.40-E89.5,N50.0,N83.311-N83.319,N83.331-N83.339,N95.0-N95.9,N98.1,Q50.01-Q50.39,Q55.4,Q96.0-Q96.8,Q98.0-Q98.4,Z79.890  
CPT: 54520,54660,54690,58300,58301,58660-58662,58740,58940,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9558
- Line: 468**  
Condition: ENCOPRESIS NOT DUE TO A PHYSIOLOGICAL CONDITION (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F98.1  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99324-99357,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0038,H0045,H2010,H2012-H2014,H2021,H2022,H2027,H2032,S5151,S9125,S9484,T1005
- Line: 469**  
Condition: ACQUIRED PTOSIS AND OTHER EYELID DISORDERS WITH VISION IMPAIRMENT (See Guideline Notes 64,65,130)  
Treatment: PTOSIS REPAIR  
ICD-10: G90.2,H02.201-H02.519,H02.531-H02.539,Q10.0-Q10.3  
CPT: 15822,15823,67710,67875-67912,67917,67961,67971,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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- Line: 470**  
Condition: KERATOCONJUNCTIVITIS (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: A18.52,B60.12-B60.13,H16.101-H16.229,H16.251-H16.9,H18.461-H18.469,M35.01  
CPT: 67515,67880,67882,68200,68760,68761,68801-68840,92002-92014,92018-92060,92081-92136,92225,92226,92230-92310,92325-92342,92370,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 471**  
Condition: SELECTIVE MUTISM (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F94.0  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0023,H0032-H0038,H2010,H2012,H2014,H2021,H2022,H2027,H2032,H2033,S9484
- Line: 472**  
Condition: THROMBOSED AND COMPLICATED HEMORRHOIDS (See Guideline Notes 64,65)  
Treatment: HEMORRHOIDECTOMY, INCISION  
ICD-10: K64.3,K64.5  
CPT: 44391,45317,45320,45334,45335,45350,45381,45382,45398,46083,46220,46221,46250-46262,46320,46500,46610-46615,46930,46945-46947,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 473**  
Condition: CHRONIC OTITIS MEDIA; OPEN WOUND OF EAR DRUM (See Guideline Notes 51,64,65,154)  
Treatment: PE TUBES/ADENOIDECTOMY/TYMPANOPLASTY, MEDICAL THERAPY  
ICD-10: H65.20-H65.33,H65.411-H65.93,H66.10-H66.23,H66.3X1-H66.3X9,H68.001-H68.009,H68.021-H68.139,H69.00-H69.03,H70.10-H70.13,H70.90-H70.93,H72.00-H72.13,H72.2X1-H72.93,H73.10-H73.13,H73.811-H73.93,H74.01-H74.09,H74.40-H74.43,H74.8X1-H74.93,H95.111-H95.119,H95.131-H95.199,S09.20XA-S09.20XD,S09.21XA-S09.21XD,S09.22XA-S09.22XD  
CPT: 42830-42836,69209-69222,69310,69420,69421,69433-69511,69601-69650,69700,69801,69905,69910,69979,92562-92565,92571-92577,92590,92591,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 474**  
Condition: OTOSCLEROSIS (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: H80.00-H80.93  
CPT: 69650-69662,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 475**  
Condition: FOREIGN BODY IN EAR AND NOSE (See Guideline Notes 64,65)  
Treatment: REMOVAL OF FOREIGN BODY  
ICD-10: T16.1XXA-T16.1XXD,T16.2XXA-T16.2XXD,T16.9XXA-T16.9XXD,T17.0XXA-T17.0XXD,T17.1XXA-T17.1XXD  
CPT: 30300-30320,69200,69205,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 476**  
Condition: CLOSED DISLOCATIONS/FRACTURES OF NON-CERVICAL VERTEBRAL COLUMN WITHOUT NEUROLOGIC INJURY OR STRUCTURAL INSTABILITY (See Guideline Notes 6,64,65,100,109,136)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: M43.5X4-M43.5X9,M48.40XA-M48.40XG,M48.43XA-M48.43XG,M48.44XA-M48.44XG,M48.45XA-M48.45XG,M48.46XA-M48.46XG,M48.47XA-M48.47XG,M48.48XA-M48.48XG,M48.50XA-M48.50XG,M48.53XA-M48.53XG,M48.54XA-M48.54XG,M48.55XA-M48.55XG,M48.56XA-M48.56XG,M48.57XA-M48.57XG,M48.58XA-M48.58XG,M80.08XA-M80.08XG,M80.88XA-M80.88XG,M84.58XA,M84.68XA,S22.000A,S22.000D-S22.000G,S22.001A,S22.001D-S22.001G,S22.002A,S22.002D-S22.002G,S22.008A,S22.008D-S22.008G,S22.009A,S22.009D-S22.009G,S22.010A,S22.010D-S22.010G,S22.011A,S22.011D-S22.011G,S22.012A,S22.012D-S22.012G,S22.018A,S22.018D-S22.018G,S22.019A,S22.019D-S22.019G,S22.020A,S22.020D-S22.020G,S22.021A,S22.021D-S22.021G,S22.022A,S22.022D-S22.022G,S22.028A,S22.028D-S22.028G,S22.029A,S22.029D



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S22.029G,S22.030A,S22.030D-S22.030G,S22.031A,S22.031D-S22.031G,S22.032A,S22.032D-S22.032G,  
S22.038A,S22.038D-S22.038G,S22.039A,S22.039D-S22.039G,S22.040A,S22.040D-S22.040G,S22.041A,  
S22.041D-S22.041G,S22.042A,S22.042D-S22.042G,S22.048A,S22.048D-S22.048G,S22.049A,S22.049D-  
S22.049G,S22.050A,S22.050D-S22.050G,S22.051A,S22.051D-S22.051G,S22.052A,S22.052D-S22.052G,  
S22.058A,S22.058D-S22.058G,S22.059A,S22.059D-S22.059G,S22.060A,S22.060D-S22.060G,S22.061A,  
S22.061D-S22.061G,S22.062A,S22.062D-S22.062G,S22.068A,S22.068D-S22.068G,S22.069A,S22.069D-  
S22.069G,S22.070A,S22.070D-S22.070G,S22.071A,S22.071D-S22.071G,S22.072A,S22.072D-S22.072G,  
S22.078A,S22.078D-S22.078G,S22.079A,S22.079D-S22.079G,S22.080A,S22.080D-S22.080G,S22.081A,  
S22.081D-S22.081G,S22.082A,S22.082D-S22.082G,S22.088A,S22.088D-S22.088G,S22.089A,S22.089D-  
S22.089G,S22.9XXA,S23.101A-S23.101D,S23.111A-S23.111D,S23.121A-S23.121D,S23.123A-S23.123D,  
S23.131A-S23.131D,S23.133A-S23.133D,S23.141A-S23.141D,S23.143A-S23.143D,S23.151A-S23.151D,  
S23.153A-S23.153D,S23.161A-S23.161D,S23.163A-S23.163D,S23.171A-S23.171D,S23.20XA-S23.20XD,  
S23.29XA-S23.29XD,S32.000A,S32.000D-S32.000G,S32.001A,S32.001D-S32.001G,S32.008A,S32.008D-  
S32.008G,S32.009A,S32.009D-S32.009G,S32.010A,S32.010D-S32.010G,S32.011A,S32.011D-S32.011G,  
S32.018A,S32.018D-S32.018G,S32.019A,S32.019D-S32.019G,S32.020A,S32.020D-S32.020G,S32.021A,  
S32.021D-S32.021G,S32.028A,S32.028D-S32.028G,S32.029A,S32.029D-S32.029G,S32.030A,S32.030D-  
S32.030G,S32.031A,S32.031D-S32.031G,S32.038A,S32.038D-S32.038G,S32.039A,S32.039D-S32.039G,  
S32.040A,S32.040D-S32.040G,S32.041A,S32.041D-S32.041G,S32.048A,S32.048D-S32.048G,S32.049A,  
S32.049D-S32.049G,S32.050A,S32.050D-S32.050G,S32.051A,S32.051D-S32.051G,S32.058A,S32.058D-  
S32.058G,S32.059A,S32.059D-S32.059G,S32.10XA,S32.10XD-S32.10XG,S32.110A,S32.110D-S32.110G,  
S32.111A,S32.111D-S32.111G,S32.112A,S32.112D-S32.112G,S32.119A,S32.119D-S32.119G,S32.120A,  
S32.120D-S32.120G,S32.121A,S32.121D-S32.121G,S32.122A,S32.122D-S32.122G,S32.129A,S32.129D-  
S32.129G,S32.130A,S32.130D-S32.130G,S32.131A,S32.131D-S32.131G,S32.132A,S32.132D-S32.132G,  
S32.139A,S32.139D-S32.139G,S32.14XA,S32.14XD-S32.14XG,S32.15XA,S32.15XD-S32.15XG,S32.16XA,  
S32.16XD-S32.16XG,S32.17XA,S32.17XD-S32.17XG,S32.19XA,S32.19XD-S32.19XG,S33.101A-S33.101D,  
S33.111A-S33.111D,S33.121A-S33.121D,S33.131A-S33.131D,S33.141A-S33.141D,S33.2XXA-S33.2XXD,  
S33.39XA-S33.39XD,Z47.2

CPT: 20930-20938,22310,22325-22328,22510-22819,22840-22855,22859,27216,27218,29035-29046,29700,29710,  
29720,63001-63011,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-  
98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,  
99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,  
G0513,G0514

**Line: 477**  
Condition: CONDUCT DISORDER, AGE 18 OR UNDER (See Guideline Notes 54,64,65,152)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F91.0-F91.2,F91.8-F91.9  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,  
99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,  
G0514,H0004,H0017-H0019,H0023,H0032-H0034,H0036-H0039,H0045,H2010,H2012,H2014,H2021-H2023,  
H2027,H2032,H2033,S5151,S9125,S9480,S9484,T1005

**Line: 478**  
Condition: BREAST CYSTS AND OTHER DISORDERS OF THE BREAST (See Guideline Notes 64,65,149)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: N60.01-N60.99,N64.0,N64.89  
CPT: 10160,19000,19001,19110-19126,49185,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-  
99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 479**  
Condition: CYSTS OF BARTHOLIN'S GLAND AND VULVA (See Guideline Notes 64,65)  
Treatment: INCISION AND DRAINAGE, MEDICAL THERAPY  
ICD-10: N75.0,N75.8-N75.9,N76.5-N76.6,N76.81-N76.89,N77.0  
CPT: 10060,10061,11004,56440,56501,56515,56740,57135,93792,93793,98966-98969,99051,99060,99070,99078,  
99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-  
99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 480**  
Condition: LICHEN PLANUS (See Guideline Notes 21,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: L43.0-L43.9,L44.1-L44.3,L66.1  
CPT: 11900,11901,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,  
99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514



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**Line: 481**  
Condition: RUPTURE OF SYNOVIUM  
Treatment: REMOVAL OF BAKER'S CYST  
ICD-10: M66.0,M71.20-M71.22  
CPT: 27345,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 482**  
Condition: ENOPHTHALMOS (See Guideline Notes 64,65)  
Treatment: ORBITAL IMPLANT  
ICD-10: H05.401-H05.429,H11.241-H11.249  
CPT: 21076,21077,67550,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: D5915,D5928,D5992,D5993,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 483**  
Condition: BELL'S PALSY, EXPOSURE KERATOCONJUNCTIVITIS (See Guideline Notes 64,65)  
Treatment: TARSORRHAPHY  
ICD-10: G51.0-G51.9,H02.59,H02.89,H16.211-H16.219  
CPT: 15840-15842,64864-64868,67875-67882,67911,67917,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 484**  
Condition: PERIPHERAL ENTHESOPATHIES (See Guideline Notes 6,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: M25.70,M25.721-M25.749,M25.761-M25.776,M46.00-M46.09,M60.10,M60.111-M60.19,M70.10-M70.52,M75.20-M75.22,M76.40-M76.72,M76.811-M76.9,M77.00-M77.9,Z45.42  
CPT: 93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 485**  
Condition: ANGIOEDEMA (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: D81.810,T78.3XXA-T78.3XXD  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 486**  
Condition: CLOSED FRACTURE OF ONE OR MORE PHALANGES OF THE FOOT, NOT INCLUDING THE GREAT TOE  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: M84.377A-M84.377G,M84.378A-M84.378G,M84.379A-M84.379G,M84.477A-M84.477G,M84.478A-M84.478G,M84.479A-M84.479G,S92.501A,S92.501D-S92.501G,S92.502A,S92.502D-S92.502G,S92.503A,S92.503D-S92.503G,S92.504A,S92.504D-S92.504G,S92.505A,S92.505D-S92.505G,S92.506A,S92.506D-S92.506G,S92.511A,S92.511D-S92.511G,S92.512A,S92.512D-S92.512G,S92.513A,S92.513D-S92.513G,S92.514A,S92.514D-S92.514G,S92.515A,S92.515D-S92.515G,S92.516A,S92.516D-S92.516G,S92.521A,S92.521D-S92.521G,S92.522A,S92.522D-S92.522G,S92.523A,S92.523D-S92.523G,S92.524A,S92.524D-S92.524G,S92.525A,S92.525D-S92.525G,S92.526A,S92.526D-S92.526G,S92.531A,S92.531D-S92.531G,S92.532A,S92.532D-S92.532G,S92.533A,S92.533D-S92.533G,S92.534A,S92.534D-S92.534G,S92.535A,S92.535D-S92.535G,S92.536A,S92.536D-S92.536G,S92.591A,S92.591D-S92.591G,S92.592A,S92.592D-S92.592G,S92.599A,S92.599D-S92.599G,S92.901G,S92.902G,S92.909G,S92.911A,S92.911D-S92.911G,S92.912A,S92.912D-S92.912G,S92.919A,S92.919D-S92.919G,S99.201A,S99.201D-S99.201G,S99.202A,S99.202D-S99.202G,S99.209A,S99.209D-S99.209G,S99.211A,S99.211D-S99.211G,S99.212A,S99.212D-S99.212G,S99.219A,S99.219D-S99.219G,S99.221A,S99.221D-S99.221G,S99.222A,S99.222D-S99.222G,S99.229A,S99.229D-S99.229G,S99.231A,S99.231D-S99.231G,S99.232A,S99.232D-S99.232G,S99.239A,S99.239D-S99.239G,S99.241A,S99.241D-S99.241G,S99.242A,S99.242D-S99.242G,S99.249A,S99.249D-S99.249G,S99.291A,S99.291D-S99.291G,S99.292A,S99.292D-S99.292G,S99.299A,S99.299D-S99.299G  
CPT: 28510,28515,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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<b>Line:</b>	<b>487</b>
Condition:	DERMATOPHYTOSIS OF NAIL, GROIN, AND FOOT AND OTHER DERMATOMYCOSIS (See Guideline Notes 64,65)
Treatment:	MEDICAL AND SURGICAL TREATMENT
ICD-10:	B35.1,B35.3,B35.6-B35.8,B36.1-B36.9,B47.9,L08.1
CPT:	11720-11732,11750,93792,93793,96900,96902,96910-96913,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>488</b>
Condition:	CLOSED FRACTURES OF RIBS, STERNUM AND COCCYX (See Guideline Notes 64,65)
Treatment:	MEDICAL THERAPY
ICD-10:	M84.38XD-M84.38XG,M84.48XD-M84.48XG,M84.68XD-M84.68XG,S22.20XA,S22.20XD-S22.20XG,S22.21XA,S22.21XD-S22.21XG,S22.22XA,S22.22XD-S22.22XG,S22.23XA,S22.23XD-S22.23XG,S22.24XA,S22.24XD-S22.24XG,S22.31XA,S22.31XD-S22.31XG,S22.32XA,S22.32XD-S22.32XG,S22.39XA,S22.39XD-S22.39XG,S22.41XA,S22.41XD-S22.41XG,S22.42XA,S22.42XD-S22.42XG,S22.43XA,S22.43XD-S22.43XG,S22.49XA,S22.49XD-S22.49XG,S22.5XXA,S22.5XXD-S22.5XXG,S22.9XXD-S22.9XXG,S32.2XXA-S32.2XXG
CPT:	21820,27200,29200,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>489</b>
Condition:	SPASTIC DIPLEGIA (See Guideline Note 170)
Treatment:	RHIZOTOMY
ICD-10:	G80.1,Z45.49
CPT:	21720,21725,62320-62323,62350-62370,63185,63190,63295,93792,93793,95990,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>490</b>
Condition:	DENTAL CONDITIONS (E.G., PERIODONTAL DISEASE)
Treatment:	ADVANCED PERIODONTICS (E.G., SURGICAL PROCEDURES AND SPLINTING)
HCPCS:	D4240-D4245,D4260,D4261,D4268-D4321,D4381,D5982
<b>Line:</b>	<b>491</b>
Condition:	HEPATORENAL SYNDROME (See Guideline Notes 64,65)
Treatment:	MEDICAL THERAPY
ICD-10:	K76.7
CPT:	93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
<b>Line:</b>	<b>492</b>
Condition:	PARAPHILIAS AND OTHER PSYCHOSEXUAL DISORDERS (See Guideline Notes 64,65)
Treatment:	MEDICAL/PSYCHOTHERAPY
ICD-10:	F65.0-F65.4,F65.50-F65.9,F66
CPT:	90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607
HCPCS:	G0176,G0177,G0248-G0250,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0023,H0032,H0034,H0035,H2010,H2014,H2027,H2032,H2033,S9484
<b>Line:</b>	<b>493</b>
Condition:	ECTROPION AND BENIGN NEOPLASM OF EYE
Treatment:	ECTROPION REPAIR
ICD-10:	D22.10-D22.12,D23.10-D23.12,D31.00-D31.92,H02.101-H02.149,H02.871-H02.879,H11.231-H11.239
CPT:	21280,21282,67343,67700-67808,67820-67850,67880,67882,67914-67924,67950-67975,68110-68135,68320-68340,68362,68705,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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- Line: 494**  
Condition: RAYNAUD'S SYNDROME (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: I73.00,I73.89-I73.9  
CPT: 64821-64823,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 495**  
Condition: CALCIUM PYROPHOSPHATE DEPOSITION DISEASE (CPPD) AND HYDROXYAPETITE DEPOSITION DISEASE (See Guideline Notes 6,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: M11.00,M11.011-M11.09,M11.20,M11.211-M11.89  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0511,G0513,G0514,S9152
- Line: 496**  
Condition: PHIMOSIS  
Treatment: SURGICAL TREATMENT  
ICD-10: N47.0-N47.1,N47.5  
CPT: 54150-54161,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 497**  
Condition: CERUMEN IMPACTION (See Guideline Notes 64,65)  
Treatment: REMOVAL OF EAR WAX  
ICD-10: H61.20-H61.23  
CPT: 69209,69210,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 498**  
Condition: SIALOLITHIASIS, MUCOCELE, DISTURBANCE OF SALIVARY SECRETION, OTHER AND UNSPECIFIED DISEASES OF SALIVARY GLANDS (See Guideline Notes 64,65,128)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: K11.5-K11.9,R68.2  
CPT: 40810-40816,42300,42305,42330-42340,42408-42425,42440-42510,42600-42665,64611,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: D7979-D7982,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 499**  
Condition: CHRONIC CONJUNCTIVITIS, BLEPHAROCONJUNCTIVITIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: E50.6,H02.721-H02.729,H10.401-H10.409,H10.421-H10.44,H10.501-H10.9,H11.141-H11.149,H11.421-H11.429,H16.261-H16.269  
CPT: 92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 500**  
Condition: CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS (See Guideline Notes 64,65,172)  
Treatment: SPECIFIED INTERVENTIONS



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- Line: 501**  
Condition: OTHER DISORDERS OF SYNOVIUM, TENDON AND BURSA, COSTOCHONDRITIS, AND CHONDRODYSSTROPHY (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: M65.20,M65.221-M65.29,M66.10,M66.20,M66.9,M67.90,M67.911-M67.99,M70.031-M70.12,M70.31-M70.32,M70.41-M70.42,M71.10,M71.111-M71.19,M71.40,M71.421-M71.58,M71.9,M85.30,M85.311-M85.39,M89.00,M89.011-M89.09,M89.611-M89.69,M90.811-M90.89,M94.0-M94.1,M94.351-M94.8X9,Q77.8-Q77.9,Q78.4,Q78.8-Q78.9  
CPT: 20550-20553,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 502**  
Condition: ERYTHEMATOUS CONDITIONS (See Guideline Notes 21,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: H01.121-H01.129,L26,L30.4,L49.0-L49.6,L49.8-L49.9,L51.0,L51.8-L51.9,L52,L53.0-L53.9,L54,L71.0,L92.0,L93.0-L93.2,L95.1,L98.2  
CPT: 17340,17360,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 503**  
Condition: PERIPHERAL ENTHESOPATHIES (See Guideline Note 28)  
Treatment: SURGICAL TREATMENT  
ICD-10: M25.70,M25.721-M25.749,M25.761-M25.776,M46.00-M46.09,M70.10-M70.72,M75.20-M75.22,M76.40-M76.72,M76.811-M76.9,M77.00-M77.9  
CPT: 20550-20553,20600-20611,21032,23931,24105,24357-24359,25109,25447,26035,26060,26121-26180,26320,26440-26556,26565-26596,26820-26863,27060,27062,27097,27100-27122,27140-27170,27306,27307,27448-27455,27466,27468,27475-27485,27715,27730-27742,28119,64702,64704,64718-64727,64774,64856,64857,64872-64907,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 504**  
Condition: NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES (See Guideline Notes 35,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: J33.0-J33.9,J34.1,J34.81-J34.9,Q30.8,T70.1XXA-T70.1XXD  
CPT: 30000,30020,30110-30140,30200-30420,30435,30450,30465-30930,31000-31230,31237-31298,61782,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 505**  
Condition: DENTAL CONDITIONS (E.G., PULPAL PATHOLOGY, PERMANENT BICUSPID/PREMOLAR TOOTH)  
Treatment: ADVANCED ENDODONTICS (E.G., RETREATMENT OF PREVIOUS ROOT CANAL THERAPY)  
HCPCS: D3331,D3333,D3347,D3421,D3426,D3430,D3450
- Line: 506**  
Condition: CIRCUMSCRIBED SCLERODERMA (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: L94.0-L94.1,L94.3  
CPT: 11900,11901,17000-17004,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 507**  
Condition: PERIPHERAL NERVE DISORDERS (See Guideline Notes 6,64,65,133)  
Treatment: MEDICAL THERAPY  
ICD-10: G13.0,G54.0-G54.9,G55,G56.10-G56.13,G56.30-G56.93,G57.00-G57.23,G57.70-G57.93,G58.0-G58.9,G59,G61.1,G61.81-G61.89,G62.0-G62.2,G62.81-G62.89,G63-G64,M53.0,S44.00XA-S44.00XD,S44.01XA-S44.01XD,S44.02XA-S44.02XD,S44.10XA-S44.10XD,S44.11XA-S44.11XD,S44.12XA-S44.12XD,S44.20XA-S44.20XD,S44.21XA-S44.21XD,S44.22XA-S44.22XD,S44.30XA-S44.30XD,S44.31XA-S44.31XD,S44.32XA-S44.32XD,S44.40XA-S44.40XD,S44.41XA-S44.41XD,S44.42XA-S44.42XD,S54.00XA-S54.00XD,S54.01XA-S54.01XD,S54.02XA-S54.02XD,S54.10XA-S54.10XD,S54.11XA-S54.11XD,S54.12XA-S54.12XD,S54.20XA-S54.20XD,S54.21XA-S54.21XD,S54.22XA-S54.22XD,S64.00XA-S64.00XD,S64.01XA-S64.01XD,S64.02XA-S64.02XD,S64.10XA-S64.10XD,S64.11XA-S64.11XD,S64.12XA-S64.12XD,S64.20XA-S64.20XD,S64.21XA-S64.21XD,S64.22XA-S64.22XD,S64.30XA-S64.30XD,S64.31XA-S64.31XD,S64.32XA-S64.32XD,S64.40XA-S64.40XD,S64.490A-S64.490D,S64.491A-S64.491D,S64.492A-S64.492D,S64.493A-S64.493D,S64.494A-S64.494D,



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- S64.495A-S64.495D, S64.496A-S64.496D, S64.497A-S64.497D, S64.498A-S64.498D, S74.00XA-S74.00XD, S74.01XA-S74.01XD, S74.02XA-S74.02XD, S74.10XA-S74.10XD, S74.11XA-S74.11XD, S74.12XA-S74.12XD, S94.00XA-S94.00XD, S94.01XA-S94.01XD, S94.02XA-S94.02XD, S94.10XA-S94.10XD, S94.11XA-S94.11XD, S94.12XA-S94.12XD, S94.20XA-S94.20XD, S94.21XA-S94.21XD, S94.22XA-S94.22XD
- CPT: 90284, 93792, 93793, 97110, 97112, 97116, 97124, 97161-97168, 97530, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607
- HCPCS: G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514
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- Line: 508**  
Condition: DYSFUNCTION OF NASOLACRIMAL SYSTEM IN ADULTS; LACRIMAL SYSTEM LACERATION (See Guideline Notes 64, 65, 134)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: H04.001-H04.9, M35.00, P39.1, Q10.6-Q10.7  
CPT: 67880, 67882, 68420, 68520, 68530, 68720-68840, 92002-92014, 92018-92060, 92071, 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514
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- Line: 509**  
Condition: BENIGN NEOPLASM OF KIDNEY AND OTHER URINARY ORGANS (See Guideline Notes 64, 65, 96)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: D17.71, D30.00-D30.9, D3A.093  
CPT: 50542, 50543, 50545, 50546, 50562, 52224, 52282, 53260, 53265, 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514
- 
- Line: 510**  
Condition: VERTIGINOUS SYNDROMES AND OTHER DISORDERS OF VESTIBULAR SYSTEM (See Guideline Notes 64, 65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: H81.10-H81.23, H81.311-H81.93, H82.1-H82.9, H83.11-H83.19, H83.2X1-H83.2X9, H83.8X1-H83.93, T75.3XXA-T75.3XXD  
CPT: 69666, 69667, 69805, 69806, 69915, 69950, 92531-92548, 93792, 93793, 95992, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514
- 
- Line: 511**  
Condition: ESOPHAGITIS AND GERD; ESOPHAGEAL SPASM; ASYMPTOMATIC DIAPHRAGMATIC HERNIA (See Guideline Notes 64, 65, 144)  
Treatment: MEDICAL THERAPY  
ICD-10: K20.8-K20.9, K21.0-K21.9, K22.10, K22.5, K44.9, T17.218A-T17.218D, T17.318A-T17.318D, T18.118A-T18.118D  
CPT: 43180, 43229, 43248, 43249, 43255, 93792, 93793, 96150-96155, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514
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- Line: 512**  
Condition: HIDRADENITIS SUPPURATIVA; DISSECTING CELLULITIS OF THE SCALP  
Treatment: MEDICAL THERAPY  
ICD-10: L66.2-L66.3, L66.8-L66.9, L73.2  
CPT: 11000, 11001, 11450-11471, 11900, 11901, 64650, 64653, 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514
- 
- Line: 513**  
Condition: CHRONIC PROSTATITIS, OTHER DISORDERS OF PROSTATE (See Guideline Notes 64, 65)  
Treatment: MEDICAL THERAPY  
ICD-10: N41.1, N41.3, N41.9, N42.0-N42.1, N42.30-N42.9  
CPT: 55801, 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99184, 99201-99239, 99281-99285, 99291-99404, 99408-99449, 99468-99480, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514



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**Line: 514**  
Condition: PHLEBITIS AND THROMBOPHLEBITIS, SUPERFICIAL (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: I80.00-I80.03,I80.3-I80.9,I82.711-I82.719,I82.811-I82.819,I83.10-I83.12,I87.021-I87.029,I87.321-I87.329,Z79.01  
CPT: 29584,36465,36466,36470-36479,37500,37700-37785,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 515**  
Condition: DISORDERS OF SWEAT GLANDS (See Coding Specification Below) (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: L30.1,L74.0-L74.4,L74.510-L74.9,L75.0-L75.9,R61  
CPT: 11450-11471,64650,64653,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Chemodenervation with botulinum toxin injection (CPT 64650, 64653) is included on this line for the treatment of axillary hyperhidrosis and palmar hyperhidrosis (ICD-10 L74.52, R61)

**Line: 516**  
Condition: PARALYSIS OF VOCAL CORDS OR LARYNX (See Guideline Notes 64,65,141)  
Treatment: INCISION/EXCISION/ENDOSCOPY  
ICD-10: J38.00-J38.02,J38.6  
CPT: 31513,31551-31554,31570,31571,31574,31590,31591,92507,92508,92524,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 517**  
Condition: POSTTHROMBOTIC SYNDROME  
Treatment: MEDICAL THERAPY  
ICD-10: I87.001-I87.009,I87.021-I87.029,I87.091-I87.099  
CPT: 29584,36465-36479,37700-37761,37766-37790,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 518**  
Condition: FOREIGN BODY IN GASTROINTESTINAL TRACT WITHOUT RISK OF PERFORATION OR OBSTRUCTION  
Treatment: MEDICAL THERAPY  
ICD-10: T18.2XXA-T18.2XXD,T18.3XXA-T18.3XXD,T18.4XXA-T18.4XXD,T18.5XXA-T18.5XXD,T18.8XXA-T18.8XXD,T18.9XXA-T18.9XXD  
CPT: 43247,44363,44390,45307,45332,45379,45915,46608,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 519**  
Condition: PANNICULITIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: M35.6,M79.3  
CPT: 68760,68761,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 520**  
Condition: ROSACEA; ACNE (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: L70.0-L70.9,L71.1-L71.9,L73.0  
CPT: 10040-10061,11900,11901,17000,17340,17360,93792,93793,96900,96902,96910-96913,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514



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- Line: 521**  
Condition: SEXUAL DYSFUNCTION (See Guideline Notes 64,65,159)  
Treatment: PSYCHOTHERAPY, MEDICAL AND SURGICAL TREATMENT  
ICD-10: F10.181,F10.281,F10.981,F11.181,F11.281,F11.981,F12.188,F12.288,F12.988,F13.181,F13.281,F13.981,F14.181,F14.281,F14.981,F15.181,F15.281,F15.981,F19.181,F19.281,F19.981,F52.0-F52.1,F52.21-F52.4,F52.6-F52.9,N52.01-N52.9,N53.11-N53.19,R37  
CPT: 54235,54400-54417,90785,90832-90840,90846-90853,90882,90887,93792,93793,93980,93981,98966-98969,99051,99060,99070,99078,99201-99239,99281-99285,99291-99366,99374,99375,99379-99404,99408-99449,99471-99476,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0490,G0508-G0511,G0513,G0514,H0004,H0023,H0032-H0035,H0038,H2014,H2027,H2032,S9484
- Line: 522**  
Condition: UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER OR DIAPHRAGMATIC HERNIA) (See Guideline Notes 24,64,65)  
Treatment: REPAIR  
ICD-10: K40.20-K40.21,K40.90-K40.91,K41.20-K41.21,K41.90-K41.91,K42.9,K43.2,K43.5,K43.9,K45.8,K46.9  
CPT: 44050,49250,49505,49520,49525-49550,49555,49560,49565,49568,49570,49580,49585,49590,49650-49659,55540,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 523**  
Condition: BENIGN NEOPLASM OF NASAL CAVITIES, MIDDLE EAR AND ACCESSORY SINUSES  
Treatment: EXCISION, RECONSTRUCTION  
ICD-10: D14.0  
CPT: 30117-30150,30520,31020,31032,31201,61782,69145,69501-69554,69960,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 524**  
Condition: CHRONIC ANAL FISSURE (See Guideline Notes 52,64,65)  
Treatment: SPHINCTEROTOMY, FISSURECTOMY, FISTULECTOMY, MEDICAL THERAPY  
ICD-10: K60.1-K60.2  
CPT: 45905,45910,46020,46030,46080,46200,46270-46288,46505,46700,46706,46707,46940,46942,93792,93793,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 525**  
Condition: DEFORMITIES OF UPPER BODY AND ALL LIMBS (See Guideline Notes 64,65,94)  
Treatment: REPAIR/REVISION/RECONSTRUCTION/RELOCATION/MEDICAL THERAPY  
ICD-10: M20.001-M20.099,M21.00,M21.021-M21.079,M21.121-M21.169,M21.20,M21.211-M21.279,M21.371-M21.379,M21.519-M21.529,M21.70,M21.721-M21.959,M24.031-M24.059,M24.121-M24.159,M24.444-M24.446,M24.621-M24.659,M24.7,M24.821-M24.859,M25.10,M25.111-M25.18,M25.221-M25.269,M25.28,M25.321-M25.369,M25.80,M25.811-M25.869,M72.1,M72.4,M85.9,M89.121-M89.29,M89.70,M89.711-M89.79,M89.9,M92.00-M92.12,M92.201-M92.32,M92.8-M92.9,M93.1,M93.80,M93.811-M93.99,M94.9,M95.5-M95.8,M99.85-M99.87,M99.89,Q65.9,Q67.6,Q68.1-Q68.5,Q68.8,Q72.70,Q74.0-Q74.9,Q76.6-Q76.9,Q79.6-Q79.8  
CPT: 11042,11045,20150,20690-20694,21740-21743,24000,24006,24101,24102,25101-25109,25320,25335,25337,25390-25393,25441-25492,25810-25830,26035,26055,26060,26121-26180,26320,26390,26426,26432,26440-26556,26565-26596,26820-26863,27097,27100-27122,27140,27185,27306,27307,27435,27448-27455,27465-27468,27475-27485,27590,27656,27676,27685-27690,27705,27715,27727-27742,28300,28304,29075,29130,29345,29540,29861-29863,64702,64704,64718-64727,64774-64783,64788-64792,64856,64857,64872-64907,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 526**  
Condition: DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS (See Guideline Notes 64,65,129)  
Treatment: MEDICAL AND SURGICAL THERAPY  
ICD-10: D78.02,G43.A0-G43.A1,G43.D0-G43.D1,K30,K31.0,K31.2,K31.4,K31.83-K31.9,K58.0-K58.9,K59.00-K59.1,K59.4-K59.9,K91.0-K91.1,K91.89,P78.3,R15.0,R15.2-R15.9  
CPT: 44141-44144,44188,44206,44320,44340-44346,45110,45395,45397,46761,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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- Line: 527**  
Condition: CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS (See Guideline Notes 37,60,64,65,100,101,161)  
Treatment: SURGICAL THERAPY  
ICD-10: G95.0,M40.00-M40.15,M40.202-M40.57,M42.00-M42.9,M43.00-M43.28,M43.8X1-M43.8X9,M45.0-M45.9,M46.1,M46.40-M46.99,M47.20-M47.28,M47.811-M47.9,M48.00-M48.05,M48.061-M48.19,M48.30-M48.38,M48.8X1-M48.9,M49.80-M49.89,M50.10-M50.11,M50.120-M50.93,M51.14-M51.9,M53.80-M53.9,M54.10-M54.18,M96.1-M96.4,M99.20-M99.79,Q06.0-Q06.3,Q06.8-Q06.9,Q76.0-Q76.2,Q76.411-Q76.49,S13.0XXA-S13.0XXD,S23.0XXA-S23.0XXD,S23.100A-S23.100D,S23.110A-S23.110D,S23.120A-S23.120D,S23.122A-S23.122D,S23.130A-S23.130D,S23.132A-S23.132D,S23.140A-S23.140D,S23.142A-S23.142D,S23.150A-S23.150D,S23.152A-S23.152D,S23.160A-S23.160D,S23.162A-S23.162D,S23.170A-S23.170D,S33.0XXA-S33.0XXD,S33.100A-S33.100D,S33.110A-S33.110D,S33.120A-S33.120D,S33.130A-S33.130D,S33.140A-S33.140D,S34.3XXA-S34.3XXD  
CPT: 20610,20660-20665,20930-20938,21720,21725,22206-22226,22532-22865,27035,27096,27279,29000-29046,29710,29720,62287,62322,62323,63001-63091,63170,63173-63200,63270-63273,63295-63610,63650,63655,63685,64483,64484,64493-64495,93792,93793,96150-96155,97110-97124,97140-97168,97530,97535,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487,99489,99495,99496,99605-99607  
HCPCS: G0157-G0160,G0248-G0250,G0260,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0508-G0511,G0513,G0514,S2350,S2351
- Line: 528**  
Condition: FIBROMYALGIA, CHRONIC FATIGUE SYNDROME, AND RELATED DISORDERS (See Guideline Notes 64,65,135)  
Treatment: MEDICAL THERAPY  
ICD-10: G89.21,G89.28-G89.29,G89.4,M79.7,R53.82  
CPT: 90785,90832-90840,90846-90853,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 529**  
Condition: CHRONIC PELVIC INFLAMMATORY DISEASE, PELVIC PAIN SYNDROME, DYSpareunia (See Guideline Notes 55,64,65,110)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: N70.11-N70.93,N71.1-N71.9,N73.1-N73.2,N73.4-N73.9,N74,N83.8,N94.0,N94.10-N94.2,N94.810-N94.89,R10.2  
CPT: 49322,58150,58180,58260,58262,58290,58291,58400,58410,58541-58544,58550-58554,58562,58570-58573,58660-58662,58700-58740,58805,58925,58940,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 530**  
Condition: MILD ECZEMA (See Guideline Notes 21,64,65,156)  
Treatment: MEDICAL THERAPY  
ICD-10: E08.620,E09.620,E10.620,E11.620,E13.620,L20.0,L20.81-L20.9,Z51.6  
CPT: 86003,86008,86486,93792,93793,95004,95018-95180,96900,96902,96910-96913,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 531**  
Condition: CONTACT DERMATITIS AND NON-INFECTIOUS OTITIS EXTERNA (See Guideline Notes 64,65,156)  
Treatment: MEDICAL THERAPY  
ICD-10: H60.501-H60.93,L23.0-L23.7,L23.81-L23.9,L24.0-L24.7,L24.81-L24.9,L25.0-L25.9,L30.0,L30.2,L30.8-L30.9,L56.0-L56.4,L56.8-L56.9,L57.1,L57.5-L57.9,L58.0-L58.9,L59.0-L59.9,Z51.6  
CPT: 86003,86008,86486,93792,93793,95004,95018-95180,96900,96902,96910-96913,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 532**  
Condition: HYPOTENSION (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: G90.01,I95.0-I95.3,I95.81-I95.9  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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**Line: 533**  
Condition: VIRAL, SELF-LIMITING ENCEPHALITIS, MYELITIS AND ENCEPHALOMYELITIS (See Guideline Notes 61,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A81.89-A81.9,A83.0-A83.9,A84.0-A84.9,A85.0-A85.1,A85.8,A86,B01.11-B01.12,B05.0,B06.00-B06.09,B06.82,G04.81-G04.91,G05.3-G05.4,G37.4  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 534**  
Condition: PERIPHERAL NERVE DISORDERS (See Guideline Note 133)  
Treatment: SURGICAL TREATMENT  
ICD-10: G54.0-G54.4,G54.6-G54.9,G55,G56.10-G56.13,G56.30-G56.93,G57.00-G57.23,G57.70-G57.93,G58.0-G58.9,M53.0,S44.00XA-S44.00XD,S44.01XA-S44.01XD,S44.02XA-S44.02XD,S44.10XA-S44.10XD,S44.11XA-S44.11XD,S44.12XA-S44.12XD,S44.20XA-S44.20XD,S44.21XA-S44.21XD,S44.22XA-S44.22XD,S44.30XA-S44.30XD,S44.31XA-S44.31XD,S44.32XA-S44.32XD,S44.40XA-S44.40XD,S44.41XA-S44.41XD,S44.42XA-S44.42XD,S54.00XA-S54.00XD,S54.01XA-S54.01XD,S54.02XA-S54.02XD,S54.10XA-S54.10XD,S54.11XA-S54.11XD,S54.12XA-S54.12XD,S54.20XA-S54.20XD,S54.21XA-S54.21XD,S54.22XA-S54.22XD,S64.00XA-S64.00XD,S64.01XA-S64.01XD,S64.02XA-S64.02XD,S64.10XA-S64.10XD,S64.11XA-S64.11XD,S64.12XA-S64.12XD,S64.20XA-S64.20XD,S64.21XA-S64.21XD,S64.22XA-S64.22XD,S64.30XA-S64.30XD,S64.31XA-S64.31XD,S64.32XA-S64.32XD,S64.40XA-S64.40XD,S64.490A-S64.490D,S64.491A-S64.491D,S64.492A-S64.492D,S64.493A-S64.493D,S64.494A-S64.494D,S64.495A-S64.495D,S64.496A-S64.496D,S64.497A-S64.497D,S64.498A-S64.498D,S74.00XA-S74.00XD,S74.01XA-S74.01XD,S74.02XA-S74.02XD,S74.10XA-S74.10XD,S74.11XA-S74.11XD,S74.12XA-S74.12XD,S94.00XA-S94.00XD,S94.01XA-S94.01XD,S94.02XA-S94.02XD,S94.10XA-S94.10XD,S94.11XA-S94.11XD,S94.12XA-S94.12XD,S94.20XA-S94.20XD,S94.21XA-S94.21XD,S94.22XA-S94.22XD  
CPT: 23397,64702-64719,64722-64727,64774-64792,64820,64856,64857,64872-64907,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 535**  
Condition: DENTAL CONDITIONS (E.G., PULPAL PATHOLOGY, PERMANENT MOLAR TOOTH)  
Treatment: ADVANCED ENDODONTICS (E.G., RETREATMENT OF PREVIOUS ROOT CANAL THERAPY)  
HCPCS: D3331,D3333,D3348,D3425,D3426,D3430,D3450

**Line: 536**  
Condition: ICHTHYOSIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: Q80.0-Q80.9  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 537**  
Condition: LESION OF PLANTAR NERVE; PLANTAR FASCIAL FIBROMATOSIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY, EXCISION  
ICD-10: G57.60-G57.63,M72.2  
CPT: 20550,28008,28060,28080,29893,64455,64632,64726,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 538**  
Condition: TENSION HEADACHES (See Coding Specification Below) (See Guideline Notes 64,65,92)  
Treatment: MEDICAL THERAPY  
ICD-10: G44.201-G44.52,G44.59-G44.89,M99.80,R51  
CPT: 93792,93793,97810-98942,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

Osteopathic manipulative treatment and chiropractic manipulative treatment (CPT 98926-98929, 98940- 98943) pair on this line only with cervicogenic headache (R51).



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- Line: 539**  
Condition: MILD PSORIASIS; DERMATOPHYTOSIS: SCALP, HAND, BODY (See Guideline Notes 21,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: B35.0,B35.2,B35.4-B35.5,B35.9,L40.0-L40.4,L40.8-L40.9,L41.0-L41.9,L44.0,L94.5  
CPT: 11900,11901,93792,93793,96900,96902,96910-96922,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 540**  
Condition: DEFORMITIES OF FOOT (See Guideline Notes 64,65,158)  
Treatment: FASCIOTOMY/INCISION/REPAIR/ARTHRODESIS  
ICD-10: M20.10-M20.12,M20.30-M20.42,M20.5X1-M20.62,M21.171-M21.172,M21.531-M21.6X9,M21.961-M21.969,M24.074-M24.076,M24.477-M24.479,M24.674-M24.676,M24.873,M24.876,M25.271-M25.279,M25.371-M25.376,M92.60-M92.72,Q66.80-Q66.9,Q72.70,Q74.2  
CPT: 27612,27690-27692,28008,28010,28035,28050-28072,28086-28092,28110-28119,28126-28160,28220-28289,28292-28341,28360,28705-28730,28737-28760,29405,29425,29450,29750,29904-29907,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 541**  
Condition: FOREIGN BODY GRANULOMA OF MUSCLE, SKIN AND SUBCUTANEOUS TISSUE (See Guideline Notes 64,65)  
Treatment: REMOVAL OF GRANULOMA  
ICD-10: L92.3,M60.20,M60.211-M60.28  
CPT: 21011-21014,21552-21556,21930-21933,22901-22903,23071-23076,24071-24076,25071-25076,26111-26116,27043-27048,27327,27328,27337,27339,27618,27619,27632,27634,28039-28045,28192,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 542**  
Condition: HYDROCELE (See Guideline Notes 64,65,149)  
Treatment: MEDICAL THERAPY, EXCISION  
ICD-10: N43.3,N43.40-N43.42,N50.89,P83.5  
CPT: 49185,54840,55000-55060,55500,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 543**  
Condition: SYMPTOMATIC URTICARIA (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: L50.0-L50.1,L50.5-L50.8,T78.1XXA-T78.1XXD  
CPT: 86003,86008,93792,93793,96900,96902,96910-96913,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 544**  
Condition: IMPULSE DISORDERS (See Guideline Notes 58,64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F63.1-F63.2,F63.81-F63.9  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0017-H0019,H0023,H0032-H0034,H0036-H0039,H0045,H2010,H2013,H2014,H2021-H2023,H2027,H2032,S5151,S9125,S9484,T1005
- Line: 545**  
Condition: SUBLINGUAL, SCROTAL, AND PELVIC VARICES (See Guideline Notes 64,65)  
Treatment: VENOUS INJECTION, VASCULAR SURGERY  
ICD-10: I86.0-I86.2  
CPT: 36470,37241,37242,55530,55535,55550,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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**Line: 546**  
Condition: ASEPTIC MENINGITIS (See Guideline Notes 61,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A87.0-A87.9,A88.0,A88.8,A89,B01.0,B05.1,G02,G03.2  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 547**  
Condition: TMJ DISORDER (See Guideline Notes 64,65)  
Treatment: TMJ SPLINTS  
ICD-10: M26.601-M26.69,S03.40XA-S03.40XD,S03.41XA-S03.41XD,S03.42XA-S03.42XD,S03.43XA-S03.43XD  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: D7880,D7881,G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 548**  
Condition: CHRONIC DISEASE OF TONSILS AND ADENOIDS (See Guideline Notes 36,64,65)  
Treatment: TONSILLECTOMY AND ADENOIDECTOMY  
ICD-10: J35.01-J35.9  
CPT: 42820-42836,42860,42870,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 549**  
Condition: SOMATIC SYMPTOMS AND RELATED DISORDERS (See Guideline Notes 64,65)  
Treatment: CONSULTATION  
ICD-10: F44.0-F44.7,F44.81-F44.9,F45.0-F45.1,F45.20-F45.9,F52.5,F68.10-F68.13  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,96150-96155,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0017,H0019,H0023,H0032-H0039,H2010,H2012-H2014,H2021-H2023,H2027,H2032,H2033,S9484

**Line: 550**  
Condition: OTHER NONINFECTIOUS GASTROENTERITIS AND COLITIS (See Guideline Notes 61,64,65,156)  
Treatment: MEDICAL THERAPY  
ICD-10: K52.1,K52.21-K52.29,K52.81-K52.82,K52.831-K52.9,K90.9,Z51.6  
CPT: 86003,86008,86486,93792,93793,95004,95018-95180,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 551**  
Condition: HEMATOMA OF AURICLE OR PINNA AND HEMATOMA OF EXTERNAL EAR (See Guideline Notes 64,65)  
Treatment: DRAINAGE  
ICD-10: H61.101-H61.199,H61.811-H61.899,M95.10-M95.12  
CPT: 10140,69000-69020,69140,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 552**  
Condition: OTHER HYPERTROPHIC OR ATROPHIC CONDITIONS OF SKIN (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: H01.111-H01.119,H01.131-H01.149,L11.0,L11.8-L11.9,L21.0-L21.9,L28.0-L28.2,L29.0-L29.9,L30.3,L57.2,L57.4,L66.4,L83,L85.0-L85.2,L85.8-L85.9,L86,L87.0-L87.9,L90.1-L90.4,L90.6-L90.9,L91.8-L91.9,L92.2,L94.8-L94.9,L98.1,L98.5-L98.6  
CPT: 11000-11057,11200,11201,11401-11406,11900,11950-11954,17000-17004,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514



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- Line: 553**  
Condition: CHONDROMALACIA (See Guideline Notes 6,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: M94.20,M94.211-M94.29  
CPT: 93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 554**  
Condition: CYST OF KIDNEY, ACQUIRED (See Guideline Notes 64,65,149)  
Treatment: MEDICAL THERAPY  
ICD-10: N28.1  
CPT: 49185,50390,50541,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 555**  
Condition: DYSMENORRHEA (See Guideline Notes 59,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: N94.4-N94.6  
CPT: 58150,58180,58260,58290,58541-58544,58550-58554,58570-58573,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 556**  
Condition: BENIGN NEOPLASM OF BONE AND ARTICULAR CARTILAGE INCLUDING OSTEOID OSTEOMAS; BENIGN NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE (See Guideline Notes 6,7,11,64,65,100,137)  
Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY  
ICD-10: D16.00-D16.9,D17.79,D18.09,D21.0,D21.10-D21.9,D36.10-D36.17,D48.1,D61.810,G89.3,K09.0-K09.1,M12.20,M12.211-M12.29,M27.1,M27.40-M27.49,M27.8,M67.80,M67.811-M67.89,M85.00,M85.011-M85.09,M85.40,M85.411-M85.69,Z51.0,Z51.12  
CPT: 11400-11446,12051,12052,13131,17106-17111,20150,20550,20551,20600-20611,20615,20930-20938,20955-20973,21011-21014,21025-21032,21040,21046-21049,21181,21198,21552-21556,21600,21930-21936,22532-22819,22853,22854,22859,23071-23076,23101-23106,23140-23156,23200,24071-24079,24102-24126,24420,24498,25000,25071,25073,25105,25110-25136,25170-25240,25295-25301,25320,25335,25337,25390-25393,25441-25447,25450-25492,25810-25830,26100-26116,26130,26200-26215,26250-26262,26449,27025,27043-27049,27054,27059,27065-27078,27187,27327,27328,27334-27339,27355-27358,27365,27465-27468,27495,27625-27638,27645-27647,27656,27745,28039-28045,28070,28072,28100-28108,28122,28124,28171-28175,28820,28825,29820,29821,29835,29836,29844,29845,29863,29875,29876,29895,29905,32553,36680,49411,63081-63103,64774,64792,77014,77261-77295,77300-77307,77331-77338,77385-77387,77401-77427,77469,77470,79005-79445,93792,93793,96377,96405,96406,96420-96440,96450,96542,96549,96570,96571,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017
- Line: 557**  
Condition: SPASTIC DYSPHONIA (See Coding Specification Below) (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: J38.3  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514,S2340,S2341  
  
ICD-10 J38.3 is included on Line 206 for treatment of abscesses and cellulitis of the vocal cords; it is included on Line 557 for treatment of spastic dysphonia.
- Line: 558**  
Condition: MACROMASTIA (See Guideline Note 166)  
Treatment: BREAST REDUCTION  
ICD-10: N62  
CPT: 19318,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



*PRIORITIZED LIST OF HEALTH SERVICES  
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**Line: 559**  
Condition: ALLERGIC RHINITIS AND CONJUNCTIVITIS, CHRONIC RHINITIS (See Guideline Notes 64,65,156)  
Treatment: MEDICAL THERAPY  
ICD-10: H10.011-H10.239,H10.411-H10.419,H10.45,H11.111-H11.129,J30.0-J30.5,J30.81-J30.9,J31.0-J31.2,T78.40XA-T78.40XD,T78.49XA-T78.49XD,Z51.6  
CPT: 30420,86003,86008,86486,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,95004,95018-95180,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 560**  
Condition: CANCER OF LIVER AND INTRAHEPATIC BILE DUCTS  
Treatment: LIVER TRANSPLANT  
ICD-10: C22.0-C22.8,T86.40-T86.49,Z48.23,Z51.11,Z52.6  
CPT: 47133-47147,86825-86835,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 561**  
Condition: BENIGN NEOPLASM AND CONDITIONS OF EXTERNAL FEMALE GENITAL ORGANS  
Treatment: EXCISION  
ICD-10: D28.0-D28.1,D28.7-D28.9,I86.3,N89.9  
CPT: 56440,56441,56501,57130,57135,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 562**  
Condition: HORDEOLUM AND OTHER DEEP INFLAMMATION OF EYELID; CHALAZION (See Guideline Notes 64,65)  
Treatment: INCISION AND DRAINAGE, MEDICAL THERAPY  
ICD-10: H00.011-H00.029,H00.11-H00.19,H02.70,H02.79,H02.821-H02.829,H02.861-H02.869  
CPT: 67700,67800-67808,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 563**  
Condition: ACUTE ANAL FISSURE (See Guideline Notes 64,65)  
Treatment: FISSURECTOMY, MEDICAL THERAPY  
ICD-10: K60.0  
CPT: 46200,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 564**  
Condition: PLEURISY (See Guideline Notes 64,65,149)  
Treatment: MEDICAL THERAPY  
ICD-10: J92.0-J92.9,J94.1,J94.8-J94.9,R09.1  
CPT: 32200-32310,32550,32552,32560-32562,32650-32652,32655,32664,32665,32940,49185,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 565**  
Condition: PERITONEAL ADHESION  
Treatment: SURGICAL TREATMENT  
ICD-10: K66.0,K66.8-K66.9,K68.9,N99.4  
CPT: 44005,44180,44603,44604,49423,58660-58662,58740,58940,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



*PRIORITIZED LIST OF HEALTH SERVICES  
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**Line: 566**  
Condition: DERMATITIS DUE TO SUBSTANCES TAKEN INTERNALLY (See Guideline Notes 64,65,156)  
Treatment: MEDICAL THERAPY  
ICD-10: L27.1-L27.9,Z51.6  
CPT: 86003,86008,86486,93792,93793,95004,95018-95180,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 567**  
Condition: BLEPHARITIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: H01.001-H01.029,H01.8-H01.9,H02.831-H02.839  
CPT: 92002-92014,92018-92060,92071,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 568**  
Condition: UNSPECIFIED URINARY OBSTRUCTION AND BENIGN PROSTATIC HYPERPLASIA WITHOUT OBSTRUCTION (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: N40.0,N40.2-N40.3  
CPT: 52450,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 569**  
Condition: OTHER COMPLICATIONS OF A PROCEDURE (See Guideline Notes 6,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: H18.821-H18.829,T81.81XA-T81.81XD,T81.82XA-T81.82XD,T81.9XXA-T81.9XXD  
CPT: 38300-38382,38542-38555,38700-38745,38747,38760,49062,49323,49423,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 570**  
Condition: ANEMIAS DUE TO DISEASE (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: D61.811,D63.0-D63.8,D64.9  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 571**  
Condition: PERSONALITY DISORDERS EXCLUDING BORDERLINE AND SCHIZOTYPAL (See Guideline Notes 64,65)  
Treatment: MEDICAL/PSYCHOTHERAPY  
ICD-10: F60.0-F60.2,F60.4-F60.7,F60.81-F60.9,F68.8,F69  
CPT: 90846,90849,90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99215,99224-99226,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0176,G0177,G0248-G0250,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0023,H0032-H0034,H0036-H0039,H0045,H2010,H2014,H2021-H2023,H2027,H2032,H2033,S5151,S9484,T1005

**Line: 572**  
Condition: ACUTE NON-SUPPURATIVE LABYRINTHITIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: H83.01-H83.09  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



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**Line: 573**  
Condition: DEVIATED NASAL SEPTUM, ACQUIRED DEFORMITY OF NOSE, OTHER DISEASES OF UPPER RESPIRATORY TRACT (See Guideline Notes 64,65)  
Treatment: EXCISION OF CYST/RHINECTOMY/PROSTHESIS  
ICD-10: J34.2-J34.3,M95.0,Q30.8,S02.2XXA,S02.2XXD-S02.2XXG,S03.1XXA-S03.1XXD  
CPT: 20912,21325-21335,30115,30117,30124-30420,30465,30520,30580,30620,30630,31020-31200,61782,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: D7260,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 574**  
Condition: STOMATITIS AND OTHER DISEASES OF ORAL SOFT TISSUES (See Guideline Notes 64,65)  
Treatment: INCISION AND DRAINAGE, MEDICAL THERAPY  
ICD-10: K12.1,K12.30-K12.39,K13.1,K13.22-K13.24,K13.4,K13.6,K13.70-K13.79,K14.0  
CPT: 40650,40805,40810-40816,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 575**  
Condition: CAVUS DEFORMITY OF FOOT; FLAT FOOT; POLYDACTYLY AND SYNDACTYLY OF TOES (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY, ORTHOTIC  
ICD-10: M21.40-M21.42,Q66.50-Q66.52,Q69.2-Q69.9,Q70.20-Q70.9  
CPT: 11200,26951,27605,27687,27690,27700-27703,28090,28238,28300,28306,28307,28344,28345,28715,28735,29907,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 576**  
Condition: INFECTIOUS MONONUCLEOSIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: B27.00-B27.99  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 577**  
Condition: URETHRITIS, NON-SEXUALLY TRANSMITTED (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: N34.2-N34.3,N36.2,N36.8-N36.9,N39.9  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 578**  
Condition: CONGENITAL ANOMALIES OF FEMALE GENITAL ORGANS EXCLUDING VAGINA (See Guideline Notes 64,65)  
Treatment: SURGICAL TREATMENT  
ICD-10: Q50.01-Q50.6,Q51.0,Q51.10-Q51.4,Q51.6,Q51.810-Q51.818,Q51.9,Q52.4  
CPT: 57135,57720,58400,58540,58559-58562,58660-58662,58700-58740,58940,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 579**  
Condition: THROMBOTIC DISORDERS  
Treatment: MEDICAL THERAPY  
ICD-10: D68.51-D68.69  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,S9345



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**Line: 580**  
Condition: CANDIDIASIS OF MOUTH, SKIN AND NAILS (See Guideline Notes 64,65,113)  
Treatment: MEDICAL THERAPY  
ICD-10: B37.0,B37.2,B37.83,B37.9,K13.0  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 581**  
Condition: BENIGN NEOPLASM OF MALE GENITAL ORGANS: TESTIS, PROSTATE, EPIDIDYMISS (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: D29.1,D29.20-D29.32,D29.8-D29.9  
CPT: 54231,54512,54522,54900,54901,55200,55600-55680,55801,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 582**  
Condition: ATROPHY OF EDENTULOUS ALVEOLAR RIDGE  
Treatment: VESTIBULOPLASTY, GRAFTS, IMPLANTS  
ICD-10: K08.20-K08.26  
CPT: 21210,21215,21244-21249,40840,40842,40845,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: D7340,D7350,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 583**  
Condition: DISEASE OF NAILS, HAIR AND HAIR FOLLICLES (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: L60.0-L60.9,L62,L63.0-L63.9,L64.0-L64.9,L65.0-L65.9,L66.0,L67.0-L67.9,L68.0-L68.9,L73.1,L73.8-L73.9,Q84.0-Q84.6  
CPT: 11000,11001,11720-11765,11900,11901,17380,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 584**  
Condition: ACUTE TONSILLITIS OTHER THAN BETA-STREPTOCOCCAL (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: J03.80-J03.91  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 585**  
Condition: CORNS AND CALLUSES (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: L84  
CPT: 11055-11057,17000-17004,17110,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514,S0390

**Line: 586**  
Condition: SYNOVITIS AND TENOSYNOVITIS (See Guideline Notes 6,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: M65.10,M65.111-M65.19,M65.30,M65.311-M65.9,M67.30,M67.311-M67.39  
CPT: 20550-20553,20600-20611,25000,26055,93792,93793,97012,97110-97124,97140-97168,97530,97535,97542,97760-97763,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES**  
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**Line: 587**  
Condition: PROLAPSED URETHRAL MUCOSA (See Guideline Notes 64,65)  
Treatment: SURGICAL TREATMENT  
ICD-10: N36.2,N36.8  
CPT: 51840,51841,52270,52285,53000,53010,53275,57220,57230,57267-57270,77321,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 588**  
Condition: DENTAL CONDITIONS (E.G., CARIES, FRACTURED TOOTH)  
Treatment: ADVANCED RESTORATIVE-ELECTIVE (INLAYS, ONLAYS, GOLD FOIL AND HIGH NOBLE METAL RESTORATIONS)  
HCPCS: D2410-D2544,D2720-D2750,D2780-D2794,D2929,D2949,D2952,D2953,D2971,D2981,D2982,D4249,D5213,D5214,D5223,D5224,D5281,D5810,D5811,D5862,D5867,D5875,D6205,D6212,D6214,D6253,D6602-D6607,D6610-D6710,D6780-D6790,D6793-D6920,D6940,D6950,D9950

**Line: 589**  
Condition: SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS (See Guideline Notes 7,11,12,64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: C26.0-C26.9,C45.7-C45.9,C7A.1-C7A.8,C7B.00-C7B.8,C76.1-C76.3,C76.40-C76.8,C77.0-C77.9,C78.00-C78.6,C78.80-C78.89,C79.81-C79.9,C80.0-C80.1,D44.9,Z85.020,Z85.030,Z85.040,Z85.060,Z85.110,Z85.230,Z85.520,Z85.821,Z85.858  
CPT: 11600-11646,32553,36260-36262,38720,38724,38745,41110-41114,41130,42120,42842-42845,43195,43196,43212-43214,43216-43229,43233,43248-43250,43266,43270,47420,47425,47610,47741,47785,49411,58951,60600-60650,61500,61510,61517-61521,61546,61548,61586,77014,77261-77295,77300-77370,77385-77387,77401-77432,77469,77470,77761-77763,77770-77790,79005-79445,93792,93793,96377,96405,96406,96420-96450,96542,96549,96570,96571,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G6001-G6017,S9537

**Line: 590**  
Condition: GANGLION (See Guideline Notes 64,65,149)  
Treatment: EXCISION  
ICD-10: M67.40,M67.411-M67.49,M71.30,M71.311-M71.39  
CPT: 10140,10160,20551-20553,20612,25111,25112,26160,28090,49185,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 591**  
Condition: EPISCLERITIS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: H15.101-H15.129  
CPT: 92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 592**  
Condition: DIAPER RASH (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: L22  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 593**  
Condition: TONGUE TIE AND OTHER ANOMALIES OF TONGUE (See Guideline Note 139)  
Treatment: FRENOTOMY, TONGUE TIE  
ICD-10: Q38.1-Q38.3  
CPT: 40819,41010,41115,92526,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514



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**Line: 594**  
Condition: INCONSEQUENTIAL CYSTS OF ORAL SOFT TISSUES (See Guideline Notes 64,65)  
Treatment: INCISION AND DRAINAGE  
ICD-10: K06.2,K06.8-K06.9,K09.8-K09.9,K11.1,K13.5  
CPT: 40800,41005-41009,41015-41018,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: D7460,D7461,G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 595**  
Condition: CONGENITAL DEFORMITIES OF KNEE (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: M67.50-M67.52,Q68.2,Q74.1  
CPT: 27403-27416,27420-27429,27435,27465-27468,27656,29871-29889,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 596**  
Condition: CHRONIC PANCREATITIS  
Treatment: SURGICAL TREATMENT  
ICD-10: K86.0-K86.1  
CPT: 48020,48120,48548,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 597**  
Condition: HERPES SIMPLEX WITHOUT COMPLICATIONS, EXCLUDING GENITAL HERPES (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: B00.1,B00.9,B10.81-B10.89  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 598**  
Condition: DENTAL CONDITIONS (E.G., MISSING TEETH)  
Treatment: COMPLEX PROSTHODONTICS (I.E., FIXED BRIDGES, OVERDENTURES)  
HCPCS: D5863-D5866,D6211,D6241,D6242,D6251,D6252,D6545,D6549,D6751,D6752,D6791,D6792

**Line: 599**  
Condition: CONGENITAL ANOMALIES OF THE EAR WITHOUT IMPAIRMENT OF HEARING; UNILATERAL ANOMALIES OF THE EAR  
Treatment: OTOPLASTY, REPAIR AND AMPUTATION  
ICD-10: Q16.2,Q17.0-Q17.9,Z01.12  
CPT: 21086,21089,69110,69300,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: D5914,D5927,D5992,D5993,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 600**  
Condition: KELOID SCAR; OTHER ABNORMAL GRANULATION TISSUE (See Guideline Note 12)  
Treatment: INTRALESIONAL INJECTIONS/DESTRUCTION/EXCISION, RADIATION THERAPY  
ICD-10: L91.0,L92.9,Z51.0  
CPT: 11200,11201,11400-11446,11900,11901,12032,17000-17004,32553,49411,77014,77261-77295,77300-77307,77331-77338,77385-77387,77401-77427,77469,77470,79005-79445,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514,G6001-G6017

**Line: 601**  
Condition: DISORDERS OF SOFT TISSUE (See Guideline Notes 64,65,149)  
Treatment: MEDICAL THERAPY  
ICD-10: M43.6,M60.80,M60.811-M60.9,M70.80,M70.811-M70.99,M72.9,M79.0-M79.2,M79.4,M79.81-M79.9,S13.5XXA-S13.5XXD,S16.8XXA-S16.8XXD,S16.9XXA-S16.9XXD,S19.9XXA-S19.9XXD,T14.8XXA-T14.8XXD,Z45.42  
CPT: 11042,11045,20550,49185,93792,93793,95990,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514



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**Line: 602**  
**Condition:** MINOR BURNS (See Guideline Notes 64,65)  
**Treatment:** MEDICAL THERAPY  
**ICD-10:** L00,L55.0-L55.1,L55.9,T20.00XA-T20.00XD,T20.011A-T20.011D,T20.012A-T20.012D,T20.019A-T20.019D,  
T20.02XA-T20.02XD,T20.03XA-T20.03XD,T20.04XA-T20.04XD,T20.05XA-T20.05XD,T20.06XA-T20.06XD,  
T20.07XA-T20.07XD,T20.09XA-T20.09XD,T20.10XA-T20.10XD,T20.111A-T20.111D,T20.112A-T20.112D,  
T20.119A-T20.119D,T20.12XA-T20.12XD,T20.13XA-T20.13XD,T20.14XA-T20.14XD,T20.15XA-T20.15XD,  
T20.16XA-T20.16XD,T20.17XA-T20.17XD,T20.19XA-T20.19XD,T20.20XA-T20.20XD,T20.211A-T20.211D,  
T20.212A-T20.212D,T20.219A-T20.219D,T20.22XA-T20.22XD,T20.23XA-T20.23XD,T20.24XA-T20.24XD,  
T20.25XA-T20.25XD,T20.26XA-T20.26XD,T20.27XA-T20.27XD,T20.29XA-T20.29XD,T20.40XA-T20.40XD,  
T20.411A-T20.411D,T20.412A-T20.412D,T20.419A-T20.419D,T20.42XA-T20.42XD,T20.43XA-T20.43XD,  
T20.44XA-T20.44XD,T20.45XA-T20.45XD,T20.46XA-T20.46XD,T20.47XA-T20.47XD,T20.49XA-T20.49XD,  
T20.50XA-T20.50XD,T20.511A-T20.511D,T20.512A-T20.512D,T20.519A-T20.519D,T20.52XA-T20.52XD,  
T20.53XA-T20.53XD,T20.54XA-T20.54XD,T20.55XA-T20.55XD,T20.56XA-T20.56XD,T20.57XA-T20.57XD,  
T20.59XA-T20.59XD,T20.60XA-T20.60XD,T20.611A-T20.611D,T20.612A-T20.612D,T20.619A-T20.619D,  
T20.62XA-T20.62XD,T20.63XA-T20.63XD,T20.64XA-T20.64XD,T20.65XA-T20.65XD,T20.66XA-T20.66XD,  
T20.67XA-T20.67XD,T20.69XA-T20.69XD,T21.00XA-T21.00XD,T21.01XA-T21.01XD,T21.02XA-T21.02XD,  
T21.03XA-T21.03XD,T21.04XA-T21.04XD,T21.05XA-T21.05XD,T21.06XA-T21.06XD,T21.07XA-T21.07XD,  
T21.09XA-T21.09XD,T21.10XA-T21.10XD,T21.11XA-T21.11XD,T21.12XA-T21.12XD,T21.13XA-T21.13XD,  
T21.14XA-T21.14XD,T21.15XA-T21.15XD,T21.16XA-T21.16XD,T21.17XA-T21.17XD,T21.19XA-T21.19XD,  
T21.20XA-T21.20XD,T21.21XA-T21.21XD,T21.22XA-T21.22XD,T21.23XA-T21.23XD,T21.24XA-T21.24XD,  
T21.25XA-T21.25XD,T21.26XA-T21.26XD,T21.27XA-T21.27XD,T21.29XA-T21.29XD,T21.40XA-T21.40XD,  
T21.41XA-T21.41XD,T21.42XA-T21.42XD,T21.43XA-T21.43XD,T21.44XA-T21.44XD,T21.45XA-T21.45XD,  
T21.46XA-T21.46XD,T21.47XA-T21.47XD,T21.49XA-T21.49XD,T21.50XA-T21.50XD,T21.51XA-T21.51XD,  
T21.52XA-T21.52XD,T21.53XA-T21.53XD,T21.54XA-T21.54XD,T21.55XA-T21.55XD,T21.56XA-T21.56XD,  
T21.57XA-T21.57XD,T21.59XA-T21.59XD,T21.60XA-T21.60XD,T21.61XA-T21.61XD,T21.62XA-T21.62XD,  
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T21.69XA-T21.69XD,T22.00XA-T22.00XD,T22.011A-T22.011D,T22.012A-T22.012D,T22.019A-T22.019D,  
T22.021A-T22.021D,T22.022A-T22.022D,T22.029A-T22.029D,T22.031A-T22.031D,T22.032A-T22.032D,  
T22.039A-T22.039D,T22.041A-T22.041D,T22.042A-T22.042D,T22.049A-T22.049D,T22.051A-T22.051D,  
T22.052A-T22.052D,T22.059A-T22.059D,T22.061A-T22.061D,T22.062A-T22.062D,T22.069A-T22.069D,  
T22.091A-T22.091D,T22.092A-T22.092D,T22.099A-T22.099D,T22.10XA-T22.10XD,T22.111A-T22.111D,  
T22.112A-T22.112D,T22.119A-T22.119D,T22.121A-T22.121D,T22.122A-T22.122D,T22.129A-T22.129D,  
T22.131A-T22.131D,T22.132A-T22.132D,T22.139A-T22.139D,T22.141A-T22.141D,T22.142A-T22.142D,  
T22.149A-T22.149D,T22.151A-T22.151D,T22.152A-T22.152D,T22.159A-T22.159D,T22.161A-T22.161D,  
T22.162A-T22.162D,T22.169A-T22.169D,T22.191A-T22.191D,T22.192A-T22.192D,T22.199A-T22.199D,  
T22.20XA-T22.20XD,T22.211A-T22.211D,T22.212A-T22.212D,T22.219A-T22.219D,T22.221A-T22.221D,  
T22.222A-T22.222D,T22.229A-T22.229D,T22.231A-T22.231D,T22.232A-T22.232D,T22.239A-T22.239D,  
T22.241A-T22.241D,T22.242A-T22.242D,T22.249A-T22.249D,T22.251A-T22.251D,T22.252A-T22.252D,  
T22.259A-T22.259D,T22.261A-T22.261D,T22.262A-T22.262D,T22.269A-T22.269D,T22.291A-T22.291D,  
T22.292A-T22.292D,T22.299A-T22.299D,T22.40XA-T22.40XD,T22.411A-T22.411D,T22.412A-T22.412D,  
T22.419A-T22.419D,T22.421A-T22.421D,T22.422A-T22.422D,T22.429A-T22.429D,T22.431A-T22.431D,  
T22.432A-T22.432D,T22.439A-T22.439D,T22.441A-T22.441D,T22.442A-T22.442D,T22.449A-T22.449D,  
T22.451A-T22.451D,T22.452A-T22.452D,T22.459A-T22.459D,T22.461A-T22.461D,T22.462A-T22.462D,  
T22.469A-T22.469D,T22.491A-T22.491D,T22.492A-T22.492D,T22.499A-T22.499D,T22.50XA-T22.50XD,  
T22.511A-T22.511D,T22.512A-T22.512D,T22.519A-T22.519D,T22.521A-T22.521D,T22.522A-T22.522D,  
T22.529A-T22.529D,T22.531A-T22.531D,T22.532A-T22.532D,T22.539A-T22.539D,T22.541A-T22.541D,  
T22.542A-T22.542D,T22.549A-T22.549D,T22.551A-T22.551D,T22.552A-T22.552D,T22.559A-T22.559D,  
T22.561A-T22.561D,T22.562A-T22.562D,T22.569A-T22.569D,T22.591A-T22.591D,T22.592A-T22.592D,  
T22.599A-T22.599D,T22.60XA-T22.60XD,T22.611A-T22.611D,T22.612A-T22.612D,T22.619A-T22.619D,  
T22.621A-T22.621D,T22.622A-T22.622D,T22.629A-T22.629D,T22.631A-T22.631D,T22.632A-T22.632D,  
T22.639A-T22.639D,T22.641A-T22.641D,T22.642A-T22.642D,T22.649A-T22.649D,T22.651A-T22.651D,  
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T22.691A-T22.691D,T22.692A-T22.692D,T22.699A-T22.699D,T23.001A-T23.001D,T23.002A-T23.002D,  
T23.009A-T23.009D,T23.011A-T23.011D,T23.012A-T23.012D,T23.019A-T23.019D,T23.021A-T23.021D,  
T23.022A-T23.022D,T23.029A-T23.029D,T23.031A-T23.031D,T23.032A-T23.032D,T23.039A-T23.039D,  
T23.041A-T23.041D,T23.042A-T23.042D,T23.049A-T23.049D,T23.051A-T23.051D,T23.052A-T23.052D,  
T23.059A-T23.059D,T23.061A-T23.061D,T23.062A-T23.062D,T23.069A-T23.069D,T23.071A-T23.071D,  
T23.072A-T23.072D,T23.079A-T23.079D,T23.091A-T23.091D,T23.092A-T23.092D,T23.099A-T23.099D,  
T23.101A-T23.101D,T23.102A-T23.102D,T23.109A-T23.109D,T23.111A-T23.111D,T23.112A-T23.112D,  
T23.119A-T23.119D,T23.121A-T23.121D,T23.122A-T23.122D,T23.129A-T23.129D,T23.131A-T23.131D,  
T23.132A-T23.132D,T23.139A-T23.139D,T23.141A-T23.141D,T23.142A-T23.142D,T23.149A-T23.149D,  
T23.151A-T23.151D,T23.152A-T23.152D,T23.159A-T23.159D,T23.161A-T23.161D,T23.162A-T23.162D,  
T23.169A-T23.169D,T23.171A-T23.171D,T23.172A-T23.172D,T23.179A-T23.179D,T23.191A-T23.191D,  
T23.192A-T23.192D,T23.199A-T23.199D,T23.201A-T23.201D,T23.202A-T23.202D,T23.209A-T23.209D,  
T23.211A-T23.211D,T23.212A-T23.212D,T23.219A-T23.219D,T23.221A-T23.221D,T23.222A-T23.222D,  
T23.229A-T23.229D,T23.231A-T23.231D,T23.232A-T23.232D,T23.239A-T23.239D,T23.241A-T23.241D,  
T23.242A-T23.242D,T23.249A-T23.249D,T23.251A-T23.251D,T23.252A-T23.252D,T23.259A-T23.259D,  
T23.261A-T23.261D,T23.262A-T23.262D,T23.269A-T23.269D,T23.271A-T23.271D,T23.272A-T23.272D,  
T23.279A-T23.279D,T23.291A-T23.291D,T23.292A-T23.292D,T23.299A-T23.299D,T23.401A-T23.401D,  
T23.402A-T23.402D,T23.409A-T23.409D,T23.411A-T23.411D,T23.412A-T23.412D,T23.419A-T23.419D,  
T23.421A-T23.421D,T23.422A-T23.422D,T23.429A-T23.429D,T23.431A-T23.431D,T23.432A-T23.432D,



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HCPCS: G0248-G0250, G0396, G0397, G0463-G0467, G0490, G0511, G0513, G0514

**Line: 603**  
Condition: DISORDERS OF SLEEP WITHOUT SLEEP APNEA (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: F10.182, F10.282, F10.982, F11.182, F11.282, F11.982, F13.182, F13.282, F13.982, F14.182, F14.282, F14.982, F15.182, F15.282, F15.982, F19.182, F19.282, F19.982, F51.01-F51.9, G25.70-G25.81, G25.89, G26, G47.00-G47.29, G47.32, G47.50-G47.51, G47.53-G47.9  
CPT: 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99201-99215, 99281-99285, 99341-99378, 99381-99404, 99408-99449, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0463-G0467, G0490, G0511, G0513, G0514

**Line: 604**  
Condition: ORAL APHTHAE (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: K12.0  
CPT: 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99201-99215, 99281-99285, 99341-99378, 99381-99404, 99408-99449, 99487-99490, 99495-99498, 99605-99607  
HCPCS: G0248-G0250, G0396, G0397, G0463-G0467, G0490, G0511, G0513, G0514



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JANUARY 1, 2018 (REVISED)

**Line: 605**  
**Condition:** SPRAINS AND STRAINS OF ADJACENT MUSCLES AND JOINTS, MINOR (See Guideline Notes 6,64,65,97,98)  
**Treatment:** MEDICAL THERAPY  
**ICD-10:** M22.2X1-M22.92,M23.000-M23.92,M24.20,M24.211-M24.28,M24.661-M24.669,Q68.6,S03.8XXA-S03.8XXD,  
S03.9XXA-S03.9XXD,S23.41XA-S23.41XD,S23.420A-S23.420D,S23.421A-S23.421D,S23.428A-S23.428D,  
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JANUARY 1, 2018 (REVISED)**

S83.241A-S83.241D,S83.242A-S83.242D,S83.249A-S83.249D,S83.261A-S83.261D,S83.262A-S83.262D,  
S83.269A-S83.269D,S83.271A-S83.271D,S83.272A-S83.272D,S83.279A-S83.279D,S83.281A-S83.281D,  
S83.282A-S83.282D,S83.289A-S83.289D,S83.30XA-S83.30XD,S83.31XA-S83.31XD,S83.32XA-S83.32XD,  
S83.401A-S83.401D,S83.402A-S83.402D,S83.409A-S83.409D,S83.411A-S83.411D,S83.412A-S83.412D,  
S83.419A-S83.419D,S83.421A-S83.421D,S83.422A-S83.422D,S83.429A-S83.429D,S83.501A-S83.501D,  
S83.502A-S83.502D,S83.509A-S83.509D,S83.511A-S83.511D,S83.512A-S83.512D,S83.519A-S83.519D,  
S83.521A-S83.521D,S83.522A-S83.522D,S83.529A-S83.529D,S83.60XA-S83.60XD,S83.61XA-S83.61XD,  
S83.62XA-S83.62XD,S83.8X1A-S83.8X1D,S83.8X2A-S83.8X2D,S83.8X9A-S83.8X9D,S83.90XA-S83.90XD,  
S83.91XA-S83.91XD,S83.92XA-S83.92XD,S86.111A-S86.111D,S86.112A-S86.112D,S86.119A-S86.119D,  
S86.211A-S86.211D,S86.212A-S86.212D,S86.219A-S86.219D,S86.311A-S86.311D,S86.312A-S86.312D,  
S86.319A-S86.319D,S86.811A-S86.811D,S86.812A-S86.812D,S86.819A-S86.819D,S86.911A-S86.911D,  
S86.912A-S86.912D,S86.919A-S86.919D,S93.401A-S93.401D,S93.402A-S93.402D,S93.409A-S93.409D,  
S93.411A-S93.411D,S93.412A-S93.412D,S93.419A-S93.419D,S93.421A-S93.421D,S93.422A-S93.422D,  
S93.429A-S93.429D,S93.431A-S93.431D,S93.432A-S93.432D,S93.439A-S93.439D,S93.501A-S93.501D,  
S93.502A-S93.502D,S93.503A-S93.503D,S93.504A-S93.504D,S93.505A-S93.505D,S93.506A-S93.506D,  
S93.509A-S93.509D,S93.511A-S93.511D,S93.512A-S93.512D,S93.513A-S93.513D,S93.514A-S93.514D,  
S93.515A-S93.515D,S93.516A-S93.516D,S93.519A-S93.519D,S93.521A-S93.521D,S93.522A-S93.522D,  
S93.523A-S93.523D,S93.524A-S93.524D,S93.525A-S93.525D,S93.526A-S93.526D,S93.529A-S93.529D,  
S93.601A-S93.601D,S93.602A-S93.602D,S93.609A-S93.609D,S93.611A-S93.611D,S93.612A-S93.612D,  
S93.619A-S93.619D,S93.621A-S93.621D,S93.622A-S93.622D,S93.629A-S93.629D,S93.691A-S93.691D,  
S93.692A-S93.692D,S93.699A-S93.699D,S96.011A-S96.011D,S96.012A-S96.012D,S96.019A-S96.019D,  
S96.111A-S96.111D,S96.112A-S96.112D,S96.119A-S96.119D,S96.211A-S96.211D,S96.212A-S96.212D,  
S96.219A-S96.219D,S96.811A-S96.811D,S96.812A-S96.812D,S96.819A-S96.819D,S96.911A-S96.911D,  
S96.912A-S96.912D,S96.919A-S96.919D

CPT: 24341,27347,27590,29240-29280,29520-29550,93792,93793,97012,97110-97124,97140-97168,97530,97535,  
97542,97760-97763,98925-98942,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-  
99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607

HCPCS: G0157-G0161,G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 606**  
Condition: ASYMPTOMATIC URTICARIA (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: L50.2-L50.4,L50.9  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,  
99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 607**  
Condition: FINGERTIP AVULSION  
Treatment: REPAIR WITHOUT PEDICLE GRAFT  
ICD-10: S61.001A-S61.001D,S61.002A-S61.002D,S61.009A-S61.009D,S61.011A-S61.011D,S61.012A-S61.012D,  
S61.019A-S61.019D,S61.031A-S61.031D,S61.032A-S61.032D,S61.039A-S61.039D,S61.051A-S61.051D,  
S61.052A-S61.052D,S61.059A-S61.059D,S61.101A-S61.101D,S61.102A-S61.102D,S61.109A-S61.109D,  
S61.111A-S61.111D,S61.112A-S61.112D,S61.119A-S61.119D,S61.131A-S61.131D,S61.132A-S61.132D,  
S61.139A-S61.139D,S61.151A-S61.151D,S61.152A-S61.152D,S61.159A-S61.159D,S61.200A-S61.200D,  
S61.201A-S61.201D,S61.202A-S61.202D,S61.203A-S61.203D,S61.204A-S61.204D,S61.205A-S61.205D,  
S61.206A-S61.206D,S61.207A-S61.207D,S61.208A-S61.208D,S61.209A-S61.209D,S61.210A-S61.210D,  
S61.211A-S61.211D,S61.212A-S61.212D,S61.213A-S61.213D,S61.214A-S61.214D,S61.215A-S61.215D,  
S61.216A-S61.216D,S61.217A-S61.217D,S61.218A-S61.218D,S61.219A-S61.219D,S61.230A-S61.230D,  
S61.231A-S61.231D,S61.232A-S61.232D,S61.233A-S61.233D,S61.234A-S61.234D,S61.235A-S61.235D,  
S61.236A-S61.236D,S61.237A-S61.237D,S61.238A-S61.238D,S61.239A-S61.239D,S61.250A-S61.250D,  
S61.251A-S61.251D,S61.252A-S61.252D,S61.253A-S61.253D,S61.254A-S61.254D,S61.255A-S61.255D,  
S61.256A-S61.256D,S61.257A-S61.257D,S61.258A-S61.258D,S61.259A-S61.259D,S61.300A-S61.300D,  
S61.301A-S61.301D,S61.302A-S61.302D,S61.303A-S61.303D,S61.304A-S61.304D,S61.305A-S61.305D,  
S61.306A-S61.306D,S61.307A-S61.307D,S61.308A-S61.308D,S61.309A-S61.309D,S61.310A-S61.310D,  
S61.311A-S61.311D,S61.312A-S61.312D,S61.313A-S61.313D,S61.314A-S61.314D,S61.315A-S61.315D,  
S61.316A-S61.316D,S61.317A-S61.317D,S61.318A-S61.318D,S61.319A-S61.319D,S61.330A-S61.330D,  
S61.331A-S61.331D,S61.332A-S61.332D,S61.333A-S61.333D,S61.334A-S61.334D,S61.335A-S61.335D,  
S61.336A-S61.336D,S61.337A-S61.337D,S61.338A-S61.338D,S61.339A-S61.339D,S61.350A-S61.350D,  
S61.351A-S61.351D,S61.352A-S61.352D,S61.353A-S61.353D,S61.354A-S61.354D,S61.355A-S61.355D,  
S61.356A-S61.356D,S61.357A-S61.357D,S61.358A-S61.358D,S61.359A-S61.359D

CPT: 12001,12002,14350,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-  
99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607

HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514



*PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)*

**Line: 608**  
Condition: ABUSE OF NONADDICTIVE SUBSTANCES  
Treatment: MEDICAL THERAPY  
ICD-10: F55.0-F55.8  
CPT: 90785,90832-90840,90846-90853,90882,90887,93792,93793,98966-98969,99051,99060,99201-99239,99324-99357,99366,99408,99409,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508-G0511,G0513,G0514,H0004-H0006,H0015,H0016,H0032-H0035,H0038,H2010,H2013,H2033,H2035,T1006,T1007,T1502

**Line: 609**  
Condition: MINOR HEAD INJURY: HEMATOMA/EDEMA WITH NO PERSISTENT SYMPTOMS (See Guideline Notes 64,65,121)  
Treatment: MEDICAL THERAPY  
ICD-10: S02.0XXA,S02.101A,S02.101D-S02.101G,S02.102A,S02.102D-S02.102G,S02.109A,S02.109D-S02.109G,S02.110A,S02.111A,S02.112A,S02.113A,S02.118A,S02.119A,S02.11AA,S02.11AD-S02.11AG,S02.11BA,S02.11BD-S02.11BG,S02.11CA,S02.11CD-S02.11CG,S02.11DA,S02.11DD-S02.11DG,S02.11EA,S02.11ED-S02.11EG,S02.11FA,S02.11FD-S02.11FG,S02.11GA,S02.11GD-S02.11GG,S02.11HA,S02.11HD-S02.11HG,S02.19XA,S02.80XA-S02.80XG,S02.91XA,S06.0X0A-S06.0X0D,S06.2X0A-S06.2X0D,S06.300A-S06.300D,S06.310A-S06.310D,S06.320A-S06.320D,S06.330A-S06.330D,S06.370A-S06.370D  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 610**  
Condition: VIRAL WARTS EXCLUDING VENEREAL WARTS (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT, CRYOSURGERY  
ICD-10: B07.0-B07.9,B08.1  
CPT: 11055-11057,11420-11424,11900,11901,17000-17004,17110,17111,28039-28043,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 611**  
Condition: ACUTE UPPER RESPIRATORY INFECTIONS AND COMMON COLD (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: J00,J06.0-J06.9  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 612**  
Condition: OTHER VIRAL INFECTIONS (See Guideline Notes 61,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: A88.1,B01.81-B01.9,B03-B04,B05.3-B05.4,B05.81-B05.9,B06.89-B06.9,B08.010-B08.09,B08.20-B08.8,B09,B25.8-B25.9,B26.0-B26.2,B26.81,B26.83-B26.9,B33.0,B33.20-B33.3,B33.8,B34.0-B34.9,B97.0,B97.10-B97.19,B97.29-B97.89  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 613**  
Condition: PHARYNGITIS AND LARYNGITIS AND OTHER DISEASES OF VOCAL CORDS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: J02.8-J02.9,J04.0,J04.30,J37.0-J37.1,J38.2  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

- Line: 614**  
Condition: ANOMALIES OF RELATIONSHIP OF JAW TO CRANIAL BASE, MAJOR ANOMALIES OF JAW SIZE, OTHER SPECIFIED AND UNSPECIFIED DENTOFACIAL ANOMALIES (See Guideline Notes 64,65)  
Treatment: OSTEOPLASTY, MAXILLA/MANDIBLE  
ICD-10: M26.00-M26.20,M26.71-M26.9,M27.0,M27.51-M27.59  
CPT: 21120-21127,21145-21160,21193-21209,21255,21295,21296,30520,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: D7940-D7949,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 615**  
Condition: DENTAL CONDITIONS (E.G., MALOCCLUSION)  
Treatment: ORTHODONTIA (I.E., FIXED AND REMOVABLE APPLIANCES AND ASSOCIATED SURGICAL PROCEDURES)  
ICD-10: M26.211-M26.29,M26.31,M26.33-M26.37,M26.4,M26.70,Z46.4  
HCPCS: D0340,D0350,D7280-D7283,D7290-D7294,D7296,D7297,D8010-D8694
- Line: 616**  
Condition: DENTAL CONDITIONS (E.G., MISSING TEETH)  
Treatment: IMPLANTS (I.E., IMPLANT PLACEMENT AND ASSOCIATED CROWN OR PROSTHESIS)  
ICD-10: M27.61-M27.69  
HCPCS: D0393-D0395,D6010-D6095,D6100-D6194,D6210,D6240,D6245,D6250,D7951,D7952
- Line: 617**  
Condition: BENIGN LESIONS OF TONGUE (See Guideline Notes 64,65)  
Treatment: EXCISION  
ICD-10: K13.21,K13.3,K14.1-K14.9  
CPT: 41110-41114,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 618**  
Condition: UNCOMPLICATED HEMORRHOIDS (See Guideline Notes 64,65)  
Treatment: HEMORRHOIDECTOMY, MEDICAL THERAPY  
ICD-10: K64.0-K64.2,K64.8-K64.9  
CPT: 44391,45317,45334,45335,45350,45381,45382,45398,46083,46220-46262,46320,46500,46610-46615,46930,46945-46947,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 619**  
Condition: PREVENTION SERVICES WITH LIMITED OR NO EVIDENCE OF EFFECTIVENESS (See Guideline Notes 64,65,106)  
Treatment: MEDICAL THERAPY  
ICD-10: Q92.61,Q95.0-Q95.1,Q95.9,Z12.12,Z12.39,Z12.5,Z12.81,Z12.83,Z13.6,Z22.0-Z22.2,Z22.31,Z22.321-Z22.322,Z22.338-Z22.9,Z71.3,Z71.42,Z71.52,Z71.82,Z79.810  
CPT: 58940,76706,90749,93792,93793,96110,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0117,G0118,G0248-G0250,G0396,G0397,G0446,G0451,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 620**  
Condition: OPEN WOUND OF INTERNAL STRUCTURES OF MOUTH WITHOUT COMPLICATION (See Guideline Notes 64,65)  
Treatment: REPAIR SOFT TISSUES  
ICD-10: K08.123,S01.501A-S01.501D,S01.502A-S01.502D,S01.512A-S01.512D,S01.532A-S01.532D,S01.552A-S01.552D  
CPT: 12001-12020,12031-12057,13131-13153,40831,41250,41251,42180,42182,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

- Line: 621**  
Condition: SEBACEOUS CYST (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: L05.91-L05.92,L72.0,L72.11-L72.9  
CPT: 10060,10061,11400-11446,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 622**  
Condition: SEBORRHEIC KERATOSIS, DYSCHROMIA, AND VASCULAR DISORDERS, SCAR CONDITIONS, AND FIBROSIS OF SKIN (See Guideline Notes 64,65)  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: E65,L11.1,L44.8-L44.9,L82.0-L82.1,L90.5,L92.1,L94.2,L94.4,L95.0,L95.8-L95.9,L98.8-L98.9,S00.241A-S00.241D,S00.242A-S00.242D,S00.249A-S00.249D  
CPT: 11000,11042,11045,11055-11057,11400-11446,13100-13160,15780-15793,15830-15839,15876-15879,17000-17108,17360,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 623**  
Condition: REDUNDANT PREPUCE (See Guideline Notes 64,65)  
Treatment: ELECTIVE CIRCUMCISION  
ICD-10: N47.3-N47.4,N47.7-N47.8,Z41.2  
CPT: 54000,54001,54150-54164,54450,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 624**  
Condition: CONJUNCTIVAL CYST (See Guideline Notes 64,65)  
Treatment: EXCISION OF CONJUNCTIVAL CYST  
ICD-10: H11.211-H11.229,H11.30-H11.33,H11.411-H11.419,H11.431-H11.449  
CPT: 68020,68040,68110,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 625**  
Condition: BENIGN NEOPLASMS OF SKIN AND OTHER SOFT TISSUES (See Guideline Notes 13,64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: D10.0-D10.2,D10.30-D10.9,D11.0-D11.9,D17.0-D17.1,D17.20-D17.6,D17.72,D17.9,D18.00-D18.01,D18.09-D18.1,D19.7-D19.9,D22.0,D22.10-D22.9,D23.0,D23.10-D23.9,D28.0-D28.9,D29.0,D29.4,D36.0,D36.7-D36.9,D3A.00,D3A.098-D3A.8,L08.9,L57.0,L92.8,L98.0  
CPT: 11400-11446,12031,12032,13100-13151,17000-17108,21011-21014,21552,21554,21931-21933,22901-22903,23071,23073,24071,24073,25071,25073,26111,26113,27043,27045,27337,27339,27632,27634,28039,28041,37241,37242,40500-40530,40810-40816,40820,41116,41826,42104-42107,42160,42808,69145,93792,93793,96567,96573,96574,96904,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: D7450-D7460,D7981,G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 626**  
Condition: DISEASE OF CAPILLARIES  
Treatment: EXCISION  
ICD-10: I78.1-I78.9,I79.8  
CPT: 11400-11426,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 627**  
Condition: BENIGN CERVICAL CONDITIONS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: N84.1,N84.3,N88.1-N88.2,N88.4-N88.9,N89.8,N90.3,N90.7,N90.89-N90.9  
CPT: 56441,56805,57061,57065,57200,57800,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514



<b>Line:</b>	<b>628</b>
Condition:	CYST, HEMORRHAGE, AND INFARCTION OF THYROID (See Guideline Notes 64,65,149)
Treatment:	SURGICAL TREATMENT
ICD-10:	E04.1,E07.89-E07.9
CPT:	49185,60200-60225,60270,60271,60300,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250, G0396, G0397, G0406-G0408, G0425-G0427, G0463-G0467, G0490, G0508-G0511, G0513, G0514

**Line: 629**  
**Condition:** PICA (See Coding Specification Below) (See Guideline Notes 64,65)  
**Treatment:** MEDICAL/PSYCHOTHERAPY  
**ICD-10:** F50.89,F98.3  
**CPT:** 90785,90832-90840,90847,93792,93793,98966-98969,99051,99060,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
**HCPCS:** G0248,G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514

Line:	630
Condition:	ACUTE VIRAL CONJUNCTIVITIS (See Guideline Notes 64,65)
Treatment:	MEDICAL THERAPY
ICD-10:	B30.0-B30.9,H10.30-H10.33
CPT:	92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607
HCPCS:	G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 631**  
**Condition:** MUSCULAR CALCIFICATION AND OSSIFICATION (See Guideline Notes 64,65)  
**Treatment:** MEDICAL THERAPY  
**ICD-10:** M61.00,M61.011-M61.9  
**CPT:** 27036,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
**HCPCS:** G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

3-22-2018 (Includes 1-5-2018 Revisions)



PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

S20.162A-S20.162D,S20.169A-S20.169D,S20.171A-S20.171D,S20.172A-S20.172D,S20.179A-S20.179D,  
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S20.222A-S20.222D,S20.229A-S20.229D,S20.301A-S20.301D,S20.302A-S20.302D,S20.309A-S20.309D,  
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S20.329A-S20.329D,S20.341A-S20.341D,S20.342A-S20.342D,S20.349A-S20.349D,S20.351A-S20.351D,  
S20.352A-S20.352D,S20.359A-S20.359D,S20.361A-S20.361D,S20.362A-S20.362D,S20.369A-S20.369D,  
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PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)

S59.902A-S59.902D, S59.909A-S59.909D, S59.911A-S59.911D, S59.912A-S59.912D, S59.919A-S59.919D, S60.00XA-S60.00XD, S60.011A-S60.011D, S60.012A-S60.012D, S60.019A-S60.019D, S60.021A-S60.021D, S60.022A-S60.022D, S60.029A-S60.029D, S60.031A-S60.031D, S60.032A-S60.032D, S60.039A-S60.039D, S60.041A-S60.041D, S60.042A-S60.042D, S60.049A-S60.049D, S60.051A-S60.051D, S60.052A-S60.052D, S60.059A-S60.059D, S60.10XA-S60.10XD, S60.111A-S60.111D, S60.112A-S60.112D, S60.119A-S60.119D, S60.121A-S60.121D, S60.122A-S60.122D, S60.129A-S60.129D, S60.131A-S60.131D, S60.132A-S60.132D, S60.139A-S60.139D, S60.141A-S60.141D, S60.142A-S60.142D, S60.149A-S60.149D, S60.151A-S60.151D, S60.152A-S60.152D, S60.159A-S60.159D, S60.211A-S60.211D, S60.212A-S60.212D, S60.219A-S60.219D, S60.221A-S60.221D, S60.222A-S60.222D, S60.229A-S60.229D, S60.311A-S60.311D, S60.312A-S60.312D, S60.319A-S60.319D, S60.321A-S60.321D, S60.322A-S60.322D, S60.329A-S60.329D, S60.341A-S60.341D, S60.342A-S60.342D, S60.349A-S60.349D, 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**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

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T07.XXXA-T07.XXXD

CPT: 10120,10140,11740,11760,11762,12001-12014,28190,93792,93793,98966-98969,99051,99060,99070,99078,  
99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607

HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 633**

Condition: CHRONIC BRONCHITIS (See Guideline Notes 64,65)

Treatment: MEDICAL THERAPY

ICD-10: J40,J41.0,J41.8,J42

CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,  
99408-99449,99487-99490,99495-99498,99605-99607

HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 634**

Condition: GALACTORRHEA, MASTODYNIA, ATROPHY, BENIGN NEOPLASMS AND UNSPECIFIED DISORDERS OF  
THE BREAST (See Guideline Notes 64,65)

Treatment: MEDICAL AND SURGICAL TREATMENT

ICD-10: D24.1-D24.9,N64.1-N64.4,N64.81-N64.82,N64.9,Q83.0-Q83.9

CPT: 19110,19120-19126,19324-19396,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,  
99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607

HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

**Line: 635**  
Condition: BENIGN POLYPS OF VOCAL CORDS (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY, STRIPPING  
ICD-10: J38.1  
CPT: 31540,31541,31572,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 636**  
Condition: BENIGN NEOPLASMS OF DIGESTIVE SYSTEM (See Guideline Notes 64,65)  
Treatment: SURGICAL TREATMENT  
ICD-10: D13.0-D13.2,D13.30-D13.6,D13.9,D17.79,D18.03,D19.1,D20.0-D20.1,D3A.010-D3A.019,D3A.092,D3A.094-D3A.096,K31.7  
CPT: 43195,43196,43212-43214,43216-43229,43233,43245,43248-43250,43266,43270,43450,44110-44120,44139-44145,44204-44208,44213,44369,44379,44381,44384,44392-44402,44404,44405,44701,45160,45308,45309,45317-45327,45333-45335,45338,45346,45347,45381-45389,46610,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 637**  
Condition: VARICOSE VEINS OF LOWER EXTREMITIES WITHOUT ULCER OR OTHER MAJOR COMPLICATION (See Guideline Notes 64,65)  
Treatment: STRIPPING/SCLEROTHERAPY, MEDICAL THERAPY  
ICD-10: I83.811-I83.93,I87.001-I87.009,I87.091-I87.309,I87.391-I87.9,I99.8-I99.9,N48.81,N50.1,R58  
CPT: 29584,36465-36479,37700-37790,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

**Line: 638**  
Condition: HYPERTELORISM OF ORBIT (See Guideline Notes 64,65)  
Treatment: ORBITOTOMY  
ICD-10: H05.89  
CPT: 67405,92002-92014,92018-92060,92081-92136,92225,92226,92230-92287,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 639**  
Condition: GALLSTONES WITHOUT CHOLECYSTITIS (See Coding Specification Below) (See Guideline Notes 64,65,167)  
Treatment: MEDICAL THERAPY, CHOLECYSTECTOMY  
ICD-10: K80.20,K80.50,K80.70,K80.80,K82.4-K82.9,K91.5  
CPT: 43260-43265,43273-43278,47490,47542,47564,47570,47600-47620,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

ICD-10 K82.8 (Other specified diseases of gallbladder) is included on Line 55 when the patient has porcelain gallbladder or gallbladder dyskinesia with a gallbladder ejection fraction <35%. Otherwise, K82.8 is included on Line 639.

**Line: 640**  
Condition: GYNECOMASTIA  
Treatment: MASTECTOMY  
ICD-10: N62  
CPT: 19300,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514

**Line: 641**  
Condition: TMJ DISORDERS (See Guideline Notes 64,65)  
Treatment: TMJ SURGERY  
ICD-10: M26.50-M26.59,M26.601-M26.69  
CPT: 20910,21010,21050-21073,21210-21243,21480-21490,29800,29804,30520,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: D7852-D7877,D7899,D7955,D7991,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514



*PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)*

- Line: 642**  
Condition: EDEMA AND OTHER CONDITIONS INVOLVING THE SKIN OF THE FETUS AND NEWBORN (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: P83.1,P83.30-P83.4,P83.6,P83.81-P83.9  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99460-99463,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 643**  
Condition: DENTAL CONDITIONS WHERE TREATMENT IS CHOSEN PRIMARILY FOR AESTHETIC CONSIDERATIONS (See Guideline Notes 64,65)  
Treatment: COSMETIC DENTAL SERVICES  
ICD-10: K00.1-K00.3,K00.5,K00.8-K00.9,K03.0-K03.1,K03.3-K03.4,K03.6-K03.7,K03.9,M26.30,M26.39  
HCPCS: D2610-D2664,D2934,D2960-D2962,D2983,D3460,D4230,D4231,D6548,D6600,D6601,D6608,D6609,D6720-D6750,D6985,D7995,D7996,D9970-D9975
- Line: 644**  
Condition: DENTAL CONDITIONS WHERE TREATMENT RESULTS IN MARGINAL IMPROVEMENT (See Guideline Notes 64,65)  
Treatment: ELECTIVE DENTAL SERVICES  
ICD-10: K00.7,K08.0,K08.51-K08.52,K08.54,K08.81-K08.89,M26.32,M85.2  
CPT: 41822  
HCPCS: D2799,D2955,D2990,D3355-D3357,D3427-D3429,D3431,D3432,D3470,D3920,D3950,D4263,D4264,D5225,D5226,D5994,D7272,D7950,D7953,D7972,D7998,D9910,D9911,D9940-D9943,D9952
- Line: 645**  
Condition: AGENESIS OF LUNG (See Guideline Notes 64,65)  
Treatment: MEDICAL THERAPY  
ICD-10: Q33.3  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 646**  
Condition: CENTRAL RETINAL ARTERY OCCLUSION  
Treatment: PARACENTESIS OF AQUEOUS  
ICD-10: H34.10-H34.13,H34.211-H34.239  
CPT: 67015,67500,67505,93792,93793,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514
- Line: 647**  
Condition: MENTAL DISORDERS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65)  
Treatment: EVALUATION  
ICD-10: F11.90,F12.90,F13.90,F14.90,F15.90,F16.90,F18.90,F19.90,F48.8,F93.8  
CPT: 93792,93793,98966-98969,99201-99215,99224,99324-99355,99366,99415,99416,99441-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514
- Line: 648**  
Condition: INTRACRANIAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65)  
Treatment: EVALUATION  
ICD-10: G45.4,G46.3-G46.8,H46.00-H46.9,H47.11-H47.12,H47.311-H47.49,H47.611-H47.649,I68.0,I68.8  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514



**PRIORITIZED LIST OF HEALTH SERVICES**  
**JANUARY 1, 2018 (REVISED)**

- Line: 649**  
Condition: INFECTIOUS DISEASES WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65)  
Treatment: EVALUATION  
ICD-10: A02.29,A80.0-A80.2,A80.30-A80.9,A82.0-A82.9,A85.2,B64,B89,B99.9,L94.6,M60.009  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 650**  
Condition: ENDOCRINE AND METABOLIC CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65)  
Treatment: EVALUATION  
ICD-10: E01.0-E01.2,E04.0,E04.2-E04.9,E16.0-E16.2,E23.7,E30.9,E32.0,E32.8-E32.9,E34.1,E34.3,E34.8-E34.9,E35,E67.1,E70.40-E70.49,E71.30,E73.1-E73.9,E74.11,E74.9,E75.10,E75.21-E75.22,E75.240-E75.249,E75.3,E75.5,E76.01-E76.1,E76.210-E76.9,E77.0,E77.8-E77.9,E78.71-E78.79,E80.4,E80.6-E80.7,E85.0,E88.89,Q89.1  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 651**  
Condition: CARDIOVASCULAR CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65,81)  
Treatment: EVALUATION  
ICD-10: I51.7,I51.89,I52,I73.1,Q24.0-Q24.1,Q25.47,Q28.9,Q34.1,Q55.5,Q89.3  
CPT: 33620,33621,75557,75565,75573,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 652**  
Condition: SENSORY ORGAN CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65,131,171)  
Treatment: EVALUATION  
ICD-10: H02.711-H02.719,H02.731-H02.739,H02.841-H02.859,H02.89-H02.9,H05.00,H05.20,H05.821-H05.9,H11.001-H11.019,H11.031-H11.10,H11.131-H11.139,H11.151-H11.159,H11.811-H11.9,H17.811-H17.89,H18.20,H18.211-H18.219,H18.231-H18.339,H18.411-H18.419,H18.461-H18.469,H18.811-H18.819,H18.891-H18.9,H21.211-H21.309,H21.9,H22,H31.001-H31.099,H31.321-H31.329,H33.111-H33.119,H33.301-H33.309,H33.321-H33.329,H34.821-H34.829,H35.40,H35.411-H35.469,H35.721-H35.739,H35.82-H35.9,H36,H43.391-H43.399,H43.89-H43.9,H44.40,H44.411-H44.419,H44.431-H44.449,H47.011-H47.099,H47.13,H47.20,H47.211-H47.299,H47.511-H47.539,H53.53-H53.55,H53.71-H53.72,H54.40,H54.413A-H54.62,H55.02,H55.04,H55.81-H55.89,H57.00-H57.04,H57.051-H57.09,H57.8-H57.9,H59.40-H59.43,H61.90-H61.93,H62.8X1-H62.8X9,H69.80-H69.83,H75.80-H75.83,H93.11-H93.19  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 653**  
Condition: NEUROLOGIC CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65)  
Treatment: EVALUATION  
ICD-10: F07.9,F48.2,G24.4,G25.82-G25.89,G31.84,G60.9,G61.9,G62.9  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 654**  
Condition: DERMATOLOGICAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 21,64,65)  
Treatment: EVALUATION  
ICD-10: B36.0,D69.2,D69.8-D69.9,E88.1,H02.60-H02.66,I73.81,L30.5,L42,L44.0,L44.4,L45,L57.3,L80,L81.0-L81.9,L85.3,L98.7,Q82.1-Q82.2,Q82.4-Q82.5,Q82.8-Q82.9,Q84.8-Q84.9  
CPT: 29581,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0429,G0463-G0467,G0490,G0511,G0513,G0514



*PRIORITIZED LIST OF HEALTH SERVICES  
JANUARY 1, 2018 (REVISED)*

- Line: 655**  
Condition: RESPIRATORY CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65,105)  
Treatment: EVALUATION  
ICD-10: J22,J98.3,J98.51-J98.9,J99,P24.10,P24.20,P24.30,Q33.1,Q33.5,Q33.8-Q33.9,Q34.0,Q34.8-Q34.9  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 656**  
Condition: GENITOURINARY CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65,72,73)  
Treatment: EVALUATION  
ICD-10: D30.8-D30.9,E28.0,K64.4,N28.81,N28.83,N28.89,N32.89-N32.9,N33,N37,N39.8,N42.30-N42.39,N44.1-N44.8,N48.6,N48.82-N48.9,N50.89-N50.9,N51,N83.321-N83.329,N83.6,N83.9,N85.4,N85.6,N85.8-N85.9,N90.60-N90.69,N90.810-N90.818,N91.4-N91.5,N93.9,N94.9,N96,N99.83,Q52.120,Q54.0,Q54.4,Q54.9,Q55.0-Q55.1,Q55.20-Q55.22,Q55.29,Q55.61-Q55.9,Q60.3,Q62.4-Q62.5,Q62.60-Q62.62,Q63.0-Q63.9,Q64.11,Q64.70,Q64.72,Q64.75,Q64.8-Q64.9,R39.81,R80.2  
CPT: 51860,51865,53080,53085,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 657**  
Condition: MUSCULOSKELETAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65)  
Treatment: EVALUATION  
ICD-10: E08.618,E09.618,E10.618,E11.618,E13.618,E78.81-E78.89,E88.2,M06.30,M07.60,M07.611-M07.69,M11.10,M11.111-M11.19,M11.9,M12.30,M12.311-M12.39,M12.80,M12.811-M12.9,M13.0,M13.10,M13.111-M13.179,M21.10,M21.179,M24.00,M24.10,M24.30,M24.40,M24.60,M24.80,M24.9,M25.20,M25.30,M35.5,M35.7,M62.00,M62.011-M62.08,M62.81,M62.831-M62.84,M62.9,M63.80,M63.811-M63.89,M84.38XD-M84.38XG,M84.811-M84.88,M85.10,M85.111-M85.19,M85.80,M85.811-M85.89,M89.30,M89.311-M89.59,M89.8X0-M89.8X9,M95.3-M95.4,M95.9,M96.0,M99.88,M99.9,Q76.5,Q77.2,Q79.9,R29.4  
CPT: 93792,93793,97010,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 658**  
Condition: GASTROINTESTINAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65)  
Treatment: EVALUATION  
ICD-10: A04.9,K11.0,K22.4,K22.9,K62.81,K62.89-K62.9,K63.89-K63.9,K75.9,K76.9,K83.5-K83.9,K86.9,K90.41,K92.9,P78.9  
CPT: 93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514
- Line: 659**  
Condition: MISCELLANEOUS CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Guideline Notes 64,65)  
Treatment: EVALUATION  
ICD-10: E66.3,E67.2,E67.8,Q18.3-Q18.9,Q30.1-Q30.9,Q67.0-Q67.4,Q67.7-Q67.8,T73.3XXA-T73.3XXD  
CPT: 40806,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487,99489,99495,99496,99605-99607  
HCPCS: G0248-G0250,G0396,G0397,G0463,G0490,G0511,G0513,G0514
- Line: 660**  
Condition: CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS (See Guideline Notes 64,65,67,173)  
Treatment: SPECIFIED INTERVENTIONS



# STATEMENTS OF INTENT



#### STATEMENT OF INTENT 1: PALLIATIVE CARE

It is the intent of the Commission that palliative care services are covered for patients with a life-threatening or serious progressive illness to alleviate symptoms and improve quality of life.

Palliative care services should include culturally appropriate discussions and medical decision making aligned with patient's personal goals of therapy, assessment of symptom burden, assistance with advance care planning, care coordination, emotional, psychosocial and spiritual support for patients and their families. Palliative care services may be provided concurrently with life prolonging/curative treatments.

Some examples of services associated with an encounter for palliative care (ICD-10 Z51.5) that should be available to patients without regard to Prioritized List line placement:

- A) Inpatient palliative care consultations
  - 1) Hospital Care E&M (CPT 99218-99233)
- B) Outpatient palliative care consultations provided in either the office or home setting
  - 1) E&M Services (CPT 99201-99215)
  - 2) Transitional Care Management Services (CPT 99495-6)
  - 3) Advance Care Planning (CPT 99497-8)
  - 4) Chronic Care Management (CPT 99487-99490)
- C) Psychological support and grief counseling (CPT 99201-99215)
- D) Medical equipment and supplies for the management of symptomatic complications or support activities of daily living
- E) Medications or acupuncture to reduce pain and symptom burden
- F) Surgical procedures or therapeutic interventions to relieve pain or symptom burden

Other services associated with palliative care includes:

- A) Social Work
- B) Clinical Chaplain/ Spiritual Care
- C) Care Coordination

It is NOT the intent of the Commission that coverage for palliative care encompasses those treatments that seek to prolong life despite substantial burdens of treatment and limited chance of benefit. See Guideline Note 12 TREATMENT OF CANCER WITH LITTLE OR NO BENEFIT.

#### STATEMENT OF INTENT 2: DEATH WITH DIGNITY ACT

It is the intent of the Commission that services under ORS 127.800-127.897 (Oregon Death with Dignity Act) be covered for those that wish to avail themselves to those services. Such services include but are not limited to attending physician visits, consulting physician confirmation, mental health evaluation and counseling, and prescription medications.

#### STATEMENT OF INTENT 3: LOWER PRIORITY SERVICES

It is the intent of the Commission that therapies that exhibit one or more of the following characteristics generally be given low priority on the Prioritized List:

- A) Marginal or clinically unimportant benefit
- B) Unproven/no benefit
- C) Harms outweigh benefits
- D) very high cost in which the cost does not justify the benefit
- E) significantly greater cost compared to alternate therapies when both have similar benefit
- F) Significant budget impact that could affect the overall Prioritized List funding level

Where possible, the Commission prioritizes pairings of condition and treatment codes to reflect this lower priority, or simply does not pair a procedure code with one or more conditions if it exhibits one of these characteristics. This is, however, impractical in several circumstances:

- A) For diagnostic services appropriate for billing with a variety of diagnoses, including diagnoses representing signs and symptoms as well as diagnoses which otherwise appear above the funding line
- B) For ancillary services such as prescription drugs, supplies, physician-administered drugs or durable medical equipment and not identified by a CPT or HCPCS code appropriate for placement on the Prioritized List
- C) For procedure codes not appropriate for placement in the funded region of the list but which may be billed with many possible diagnoses, some of which are above the funding line while others may be below the funding line

In these circumstances, the HERC identifies the services in Guideline Notes 172 and 173, which are attached to Line 500 or Line 660 in order to make its intent transparent.

#### STATEMENT OF INTENT 4: ROLE OF THE PRIORITIZED LIST IN COVERAGE

The Commission makes its prioritization decisions based on the best available published evidence about treatments for each condition. The Prioritized List prioritizes health services according to their importance for the population served and the legislature determines where to place the funding line on the Prioritized List.

The Commission recognizes that a condition and treatment pairing above the funding line does not necessarily mean that the service will be covered by the Oregon Health Plan (OHP). There may be other restrictions that apply, such as the service not being medically necessary or appropriate for an individual member. Likewise, the absence of a treatment and condition pairing above the



**STATEMENT OF INTENT 4: ROLE OF THE PRIORITIZED LIST IN COVERAGE (CONT'D)**

funding line is not meant to be an absolute exclusion from coverage. Coverage may still be authorized under applicable federal and state laws, and Oregon's Medicaid State Plan and Waiver for an individual member. For example, OAR 410-141-0480 (Oregon Health Plan Benefit Package of Covered Services) includes services such as, but not limited to, the following:

- Diagnostic services, subject to the List's diagnostic guideline notes when applicable;
- Ancillary services (such as hospitalization, durable medical equipment, certain medications and anesthesia) provided for conditions appearing above the funding line, subject to the List's ancillary guideline notes when applicable; and
- Services paired with an unfunded condition which is causing or exacerbating a funded condition, the treatments for the funded condition are not working or contraindicated, and treatment of the unfunded condition would improve the outcome of treating the funded condition (the "Comorbidity Rule" OAR 410-141-0480(8)(a through b))

In addition, Oregon's 1115(a) Waiver includes coverage for services such as, but not limited to:

- Services on unfunded lines for children ages from birth through 1
- Services provided for a condition appearing in the funded region of the List in conjunction with federal requirements for Early and Periodic Screening, Diagnosis and Treatment (EPSDT) and Oregon's waiver

As a result, the Prioritized List must be used in conjunction with applicable OHP provisions found in federal and state laws, the State Plan and Waiver in coverage determination.



# PRACTICE GUIDELINES

GUIDELINE NOTES FOR ANCILLARY AND DIAGNOSTIC SERVICES  
NOT APPEARING ON THE JANUARY 1, 2018 PRIORITIZED LIST  
OF HEALTH SERVICES

GUIDELINE NOTES FOR HEALTH SERVICES  
THAT APPEAR ON THE JANUARY 1, 2018 PRIORITIZED LIST  
OF HEALTH SERVICES



ANCILLARY/DIAGNOSTIC GUIDELINE NOTES FOR THE  
JANUARY 1, 2018 PRIORITIZED LIST OF HEALTH SERVICES (REVISED)

**ANCILLARY GUIDELINE A1, NERVE BLOCKS**

The Health Evidence Review Commission intends that single injection and continuous nerve blocks (CPT 64400-64450, 64461-64463, 64505-64530) should be covered services if they are required for successful completion of perioperative pain control for, or post-operative recovery from a covered operative procedure when the diagnosis requiring the operative procedure is also covered. Additionally, nerve blocks, are covered services for patients hospitalized with trauma, cancer, or intractable pain conditions, if the underlying condition is a covered diagnosis.

**ANCILLARY GUIDELINE A2, SELF-MONITORING OF BLOOD GLUCOSE IN DIABETES**

For patients with type 1 diabetes and those with type 2 diabetes using multiple daily insulin injections, home blood glucose monitors and related diabetic supplies are covered.

For patients with type 2 diabetes not requiring multiple daily insulin injections, 50 test strips and related supplies are covered at the time of diagnosis. For those who require diabetic medication that may result in hypoglycemia, up to 50 test strips per 90 days are covered. If there is an acute change in glycemic control or active diabetic medication adjustment, an additional 50 strips are covered.

All diabetic patients who are prescribed diabetic test strips should have a structured education and feedback program for self-monitoring of blood glucose.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**ANCILLARY GUIDELINE A3, IVC FILTERS FOR TRAUMA**

It is the intent of the Commission that inferior vena cava (IVC) filter placement (CPT 37191) and subsequent repositioning and removal (CPT 37192, 37193) are covered when medically indicated for hospitalized patients with severe trauma resulting in prolonged hospitalization.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**ANCILLARY GUIDELINE A4, SMOKING CESSATION AND ELECTIVE SURGICAL PROCEDURES**

Smoking cessation is required prior to elective surgical procedures for active tobacco users. Cessation is required for at least 4 weeks prior to the procedure and requires objective evidence of abstinence from smoking prior to the procedure.

Elective surgical procedures in this guideline are defined as surgical procedures which are flexible in their scheduling because they do not pose an imminent threat nor require immediate attention within 1 month. Reproductive (i.e. for contraceptive purposes), cancer-related and diagnostic procedures are excluded from this guideline.

The well-studied tests for confirmation of smoking cessation include cotinine levels and exhaled carbon monoxide testing. However, cotinine levels may be positive in nicotine replacement therapy (NRT) users, smokeless tobacco and e-cigarette users (which are not contraindications to elective surgery coverage). In patients using nicotine products aside from combustible cigarettes the following alternatives to urine cotinine to demonstrate smoking cessation may be considered:

- Exhaled carbon monoxide testing
- Anabasine or anatabine testing (NRT or vaping)

Certain procedures, such as lung volume reduction surgery, bariatric surgery, erectile dysfunction surgery, and spinal fusion have 6 month tobacco abstinence requirements. See Guideline Notes 8, 100, 112 and 159.

**DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE**

- A) Genetic tests are covered as diagnostic, unless they are listed below in section F1 as excluded or have other restrictions listed in this guideline. To be covered, initial screening (e.g. physical exam, medical history, family history, laboratory studies, imaging studies) must indicate that the chance of genetic abnormality is > 10% and results would do at least one of the following:
  - 1) Change treatment,
  - 2) Change health monitoring,
  - 3) Provide prognosis, or
  - 4) Provide information needed for genetic counseling for patient; or patient's parents, siblings, or children
- B) Pretest and posttest genetic counseling is required for presymptomatic and predisposition genetic testing. Pretest and posttest genetic evaluation (which includes genetic counseling) is covered when provided by a suitable trained health professional with expertise and experience in genetics.
  - 1) "Suitably trained" is defined as board certified or active candidate status from the American Board of Medical Genetics, American Board of Genetic Counseling, or Genetic Nursing Credentialing Commission.
- C) A more expensive genetic test (generally one with a wider scope or more detailed testing) is not covered if a cheaper (smaller scope) test is available and has, in this clinical context, a substantially similar sensitivity. For example, do not cover CFTR gene sequencing as the first test in a person of Northern European Caucasian ancestry because the gene panels are less expensive and provide substantially similar sensitivity in that context.



**DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE (CONT'D)**

- D) Related to genetic testing for patients with breast/ovarian and colon/endometrial cancer or other related cancers suspected to be hereditary, or patients at increased risk to due to family history.
- 1) Services are provided according to the Comprehensive Cancer Network Guidelines.
    - a) Lynch syndrome (hereditary colorectal, endometrial and other cancers associated with Lynch syndrome) services (CPT 81288, 81292-81300, 81317-81319, 81435, 81436) and familial adenomatous polyposis (FAP) services (CPT 81201-81203) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Colorectal V3.2017 (10/10/17). [www.nccn.org](http://www.nccn.org).
    - b) Breast and ovarian cancer syndrome genetic testing services (CPT 81162, 81211-81217) for women without a personal history of breast, ovarian and other associated cancers should be provided to high risk women as defined by the US Preventive Services Task Force or according to the NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and ovarian. V1.2018 (10/3/17). [www.nccn.org](http://www.nccn.org).
    - c) Breast and ovarian cancer syndrome genetic testing services (CPT 81162, 81211-81217) for women with a personal history of breast, ovarian, and other associated cancers and for men with breast cancer should be provided according to the NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast and Ovarian. V1.2018 (10/3/17). [www.nccn.org](http://www.nccn.org).
    - d) PTEN (Cowden syndrome) services (CPT 81321-81323) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Colorectal Screening. V3.2017 (10/10/17). [www.nccn.org](http://www.nccn.org).
  - 2) Genetic counseling should precede genetic testing for hereditary cancer whenever possible.
    - a) Pre and post-test genetic counseling should be covered when provided by a suitable trained health professional with expertise and experience in cancer genetics. Genetic counseling is recommended for cancer survivors when test results would affect cancer screening.
      - i) "Suitably trained" is defined as board certified or active candidate status from the American Board of Medical Genetics, American Board of Genetic Counseling, or Genetic Nursing Credentialing Commission.
    - b) If timely pre-test genetic counseling is not possible for time-sensitive cases, appropriate genetic testing accompanied by pre- and post- test informed consent and post-test disclosure performed by a board-certified physician with experience in cancer genetics should be covered.
      - i) Post-test genetic counseling should be performed as soon as is practical.
  - 3) If the mutation in the family is known, only the test for that mutation is covered. For example, if a mutation for BRCA 1 has been identified in a family, a single site mutation analysis for that mutation is covered (CPT 81215), while a full sequence BRCA 1 and 2 (CPT 81211) analyses is not. There is one exception, for individuals of Ashkenazi Jewish ancestry with a known mutation in the family, the panel for Ashkenazi Jewish BRCA mutations is covered (CPT 81212).
  - 4) Costs for rush genetic testing for hereditary breast/ovarian and colon/endometrial cancer is not covered.
  - 5) Hereditary breast cancer-related disorders genomic sequence analysis panels (CPT 81432, 81433, 81479) are only included if the panel test
    - a) Includes at least 5 genes that the NCCN Clinical Practice Guidelines in Oncology - Genetic/Familial High-Risk Assessment: Colorectal V3.2017 (10/10/17) and/or NCCN Clinical Practice Guidelines in Oncology - Genetic/Familial High-Risk Assessment: Breast and Ovarian V1.2018 (10/3/17) include(s) with specific guidance on clinical management; and,
    - b) Includes no more than a reasonable number of genes (e.g. 40 genes total).
- E) Related to diagnostic evaluation of individuals with intellectual disability (defined as a full scale or verbal IQ < 70 in an individual > age 5), developmental delay (defined as a cognitive index <70 on a standardized test appropriate for children < 5 years of age), Autism Spectrum Disorder, or multiple congenital anomalies:
- 1) CPT 81228, Cytogenomic constitutional microarray analysis for copy number variants for chromosomal abnormalities: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder.
  - 2) CPT 81229, Cytogenomic constitutional microarray analysis for copy number variants for chromosomal abnormalities; plus cytogenetic constitutional microarray analysis for single nucleotide polymorphism (SNP) variants for chromosomal abnormalities: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder; only if (a) consanguinity and recessive disease is suspected, or (b) uniparental disomy is suspected, or (c) another mechanism is suspected that is not detected by the copy number variant test alone.
  - 3) CPT 81243, 81244, Fragile X genetic testing is covered for individuals with intellectual disability/developmental delay. Although the yield of Fragile X is 3.5-10%, this is included because of additional reproductive implications.
  - 4) A visit with the appropriate specialist (often genetics, developmental pediatrics, or child neurology), including physical exam, medical history, and family history is covered. Physical exam, medical history, and family history by the appropriate specialist, prior to any genetic testing is often the most cost-effective strategy and is encouraged.
- F) Related to other tests with specific CPT codes:
- 1) Certain genetic tests have not been found to have proven clinical benefit. These tests are listed in Guideline Note 173, INTERVENTIONS THAT HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS; UNPROVEN INTERVENTIONS
  - 2) The following tests are covered only if they meet the criteria in section A above AND the specified situations:
    - a) CPT 81205, BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X): Cover only when the newborn screening test is abnormal and serum amino acids are normal
    - b) Diagnostic testing for cystic fibrosis (CF)



ANCILLARY/DIAGNOSTIC GUIDELINE NOTES FOR THE  
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**DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE (CONT'D)**

- i) CFTR, cystic fibrosis transmembrane conductance regulator tests. CPT 81220, 81222, 81223: For infants with a positive newborn screen for cystic fibrosis or who are symptomatic for cystic fibrosis, or for clients that have previously been diagnosed with cystic fibrosis but have not had genetic testing, CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics\* (CPT 81220) is covered. If two mutations are not identified, CFTR full gene sequencing (CPT 81223) is covered. If two mutations are still not identified, duplication/deletion testing (CPT 81222) is covered. These tests may be ordered as reflex testing on the same specimen.
- c) Carrier testing for cystic fibrosis
  - i) CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics\* (CPT 81220) is covered once in a lifetime.
- d) CPT 81224, CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility): Covered only after genetic counseling.
- e) CPT 81240, F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant: Factor 2 20210G>A testing should not be covered for adults with idiopathic venous thromboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.
- f) CPT 81241, F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant: Factor V Leiden testing should not be covered for: adults with idiopathic venous thromboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.
- g) CPT 81247, G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; common variant(s) (eg, A, A-) should only be covered
  - i) After G6PD enzyme activity testing is done and found to be normal; AND either
    - (a) There is an urgent clinical reason to know if a deficiency is present, e.g. in a case of acute hemolysis; OR
    - (b) In situations where the enzyme activity could be unreliable, e.g. female carrier with extreme Lyonization.
- h) CPT 81248, G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; known familial variant(s) is only covered when the information is required for genetic counseling.
- i) CPT 81249, G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; full gene sequence is only covered
  - i) after G6PD enzyme activity has been tested, and
  - ii) the requirements under CPT 81247 above have been met, and
  - iii) common variants (CPT 81247) have been tested for and not found.
- j) CPT 81256, HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D): Covered for diagnostic testing of patients with elevated transferrin saturation or ferritin levels. Covered for predictive testing ONLY when a first degree family member has treatable iron overload from HFE.
- k) CPT 81221, SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, \*S and \*Z): The alpha-1-antitrypsin protein level should be the first line test for a suspected diagnosis of AAT deficiency in symptomatic individuals with unexplained liver disease or obstructive lung disease that is not asthma or in a middle age individual with unexplained dyspnea. Genetic testing of the alpha-1 phenotype test is appropriate if the protein test is abnormal or borderline. The genetic test is appropriate for siblings of people with AAT deficiency regardless of the AAT protein test results.
- l) CPT 81415-81416, exome testing: A genetic counseling/geneticist consultation is required prior to ordering test
- m) CPT 81430-81431, Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel: Testing for mutations in GJB2 and GJB6 need to be done first and be negative in non-syndromic patients prior to panel testing.
- n) CPT 81440, 81460, 81465, mitochondrial genome testing: A genetic counseling/geneticist or metabolic consultation is required prior to ordering test.
- o) CPT 81412 Ashkenazi Jewish carrier testing panel: panel testing is only covered when the panel would replace and would be similar or lower cost than individual gene testing including CF carrier testing.

\* American College of Medical Genetics Standards and Guidelines for Clinical Genetics Laboratories. 2008 Edition, Revised 3/2011 and found at <https://www.acmg.net/StaticContent/SGs/CFTR%20Mutation%20Testing.pdf>.

**DIAGNOSTIC GUIDELINE D2, IMPLANTABLE CARDIAC LOOP RECORDERS**

Use of an implantable cardiac loop recorder (ICLR) is a covered service only when the patient meets all of the following criteria:

- 1) The evaluation is for recurrent transient loss of consciousness (TLoC); and
- 2) A comprehensive evaluation including 30 days of noninvasive ambulatory cardiac monitoring did not demonstrate a cause of the TLoC; and
- 3) A cardiac arrhythmia is suspected to be the cause of the TLoC; and
- 4) There is a likely recurrence of the TLoC within the battery longevity of the device.

ICLRs are not a covered service for evaluation of cryptogenic stroke or any other indication.

**DIAGNOSTIC GUIDELINE D3, ECHOCARDIOGRAMS WITH CONTRAST FOR CARDIAC CONDITIONS OTHER THAN CARDIAC ANOMALIES**

Need for contrast with an echocardiogram should be assessed and, if indicated, implemented at the time of the original ECHO and not as a separate procedure.



ANCILLARY/DIAGNOSTIC GUIDELINE NOTES FOR THE  
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**DIAGNOSTIC GUIDELINE D4, ADVANCED IMAGING FOR LOW BACK PAIN**

In patients with non-specific low back pain and no “red flag” conditions [see Table D4], imaging is not a covered service; otherwise work up is covered as shown in the table. Repeat imaging is only covered when there is a substantial clinical change (e.g. progressive neurological deficit) or new clinical indication for imaging (i.e. development of a new red flag condition). Repeat imaging for acute exacerbations of chronic radiculopathic pain is not covered.

Electromyography (CPT 96002-4) is not covered for non-specific low back pain.

**Table D4**  
**Low Back Pain - Potentially Serious Conditions (“Red Flags”) and Recommendations for Initial Diagnostic Work-up**

Possible cause	Key features on history or physical examination	Imaging <sup>1</sup>	Additional studies <sup>1</sup>
Cancer	<ul style="list-style-type: none"> <li>History of cancer with new onset of LBP</li> </ul>	MRI	ESR
	<ul style="list-style-type: none"> <li>Unexplained weight loss</li> <li>Failure to improve after 1 month</li> <li>Age &gt;50 years</li> <li>Symptoms such as painless neurologic deficit, night pain or pain increased in supine position</li> </ul>	Lumbosacral plain radiography	
	<ul style="list-style-type: none"> <li>Multiple risk factors for cancer present</li> </ul>	Plain radiography or MRI	
Spinal column infection	<ul style="list-style-type: none"> <li>Fever</li> <li>Intravenous drug use</li> <li>Recent infection</li> </ul>	MRI	ESR and/or CRP
Cauda equina syndrome	<ul style="list-style-type: none"> <li>Urinary retention</li> <li>Motor deficits at multiple levels</li> <li>Fecal incontinence</li> <li>Saddle anesthesia</li> </ul>	MRI	None
Vertebral compression fracture	<ul style="list-style-type: none"> <li>History of osteoporosis</li> <li>Use of corticosteroids</li> <li>Older age</li> </ul>	Lumbosacral plain radiography	None
Ankylosing spondylitis	<ul style="list-style-type: none"> <li>Morning stiffness</li> <li>Improvement with exercise</li> <li>Alternating buttock pain</li> <li>Awakening due to back pain during the second part of the night</li> <li>Younger age</li> </ul>	Anterior-posterior pelvis plain radiography	ESR and/or CRP, HLA-B27
Nerve compression/ disorders (e.g. herniated disc with radiculopathy)	<ul style="list-style-type: none"> <li>Back pain with leg pain in an L4, L5, or S1 nerve root distribution present &lt; 1 month</li> <li>Positive straight-leg-raise test or crossed straight-leg-raise test</li> </ul>	None	None
	<ul style="list-style-type: none"> <li>Radiculopathic signs<sup>2</sup> present &gt;1 month</li> <li>Severe/progressive neurologic deficits (such as foot drop), progressive motor weakness</li> </ul>	MRI <sup>3</sup>	Consider EMG/NCV
Spinal stenosis	<ul style="list-style-type: none"> <li>Radiating leg pain</li> <li>Older age</li> <li>Pain usually relieved with sitting (Pseudoclaudication a weak predictor)</li> </ul>	None	None
	<ul style="list-style-type: none"> <li>Spinal stenosis symptoms present &gt;1 month</li> </ul>	MRI <sup>3</sup>	Consider EMG/NCV

<sup>1</sup>Level of evidence for diagnostic evaluation is variable

<sup>2</sup>Radiculopathic signs are defined for the purposes of this guideline as the presence of any of the following:

- A) Markedly abnormal reflexes
- B) Segmental muscle weakness
- C) Segmental sensory loss
- D) EMG or NCV evidence of nerve root impingement
- E) Cauda equina syndrome,
- F) Neurogenic bowel or bladder
- G) Long tract abnormalities

<sup>3</sup>Only if patient is a potential candidate for surgery

Red Flag: Red flags are findings from the history and physical examination that may be associated with a higher risk of serious disorders.

CRP = C-reactive protein; EMG = electromyography; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; NCV = nerve conduction velocity.

Extracted and modified from Chou R, Qaseem A, Snow V, et al: *Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society*. Ann Intern Med. 2007; 147:478-491.



#### DIAGNOSTIC GUIDELINE D4, ADVANCED IMAGING FOR LOW BACK PAIN (CONT'D)

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

#### DIAGNOSTIC GUIDELINE D5, NEUROIMAGING FOR HEADACHE

Neuroimaging is not covered in patients with a defined tension or migraine type of headache, or a variation of their usual headache (e.g. more severe, longer in duration, or not responding to drugs).

Neuroimaging is covered for headache when a red flag\* is present.

\*The following represent red flag conditions for underlying abnormality with headache:

- A) New onset or change in headache in patients who are aged over 50
- B) Thunderclap headache: rapid time to peak headache intensity (seconds to 5 minutes)
- C) Focal neurological symptoms (e.g. limb weakness, lack of coordination, numbness or tingling)
- D) Non-focal neurological symptoms (e.g altered mental status, dizziness)
- E) Abnormal neurological examination
- F) Headache that changes with posture
- G) Headache wakening the patient up (Nota bene migraine is the most frequent cause of morning headache)
- H) Headache precipitated by physical exertion or valsalva maneuver (e.g. coughing, laughing, straining)
- I) Patients with risk factors for cerebral venous sinus thrombosis
- J) Jaw claudication
- K) Nuchal rigidity
- L) New onset headache in a patient with a history of human immunodeficiency virus (HIV) infection
- M) New onset headache in a patient with a history of cancer
- N) Cluster headache, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), or short-lasting unilateral neuralgiform headache attacks with cranial autonomic features (SUNA).

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

#### DIAGNOSTIC GUIDELINE D6, BREAST CANCER SCREENING IN ABOVE-AVERAGE RISK WOMEN

Annual screening mammography and annual screening MRI are covered only for women at above-average risk of breast cancer. This coverage, beginning at 30 years of age, includes women who have one or more of the following:

- Greater than 20% lifetime risk of breast cancer
- BRCA1 or BRCA2 gene mutation, or who have not been tested for BRCA but have a first-degree relative who is a BRCA carrier
- A personal history or a first-degree relative diagnosed with Bannayan-Riley-Ruvalcaba syndrome, Cowden syndrome, or Li-Fraumeni syndrome
- Other germline gene mutations known to confer a greater than 20% lifetime risk of breast cancer

For women with a history of high dose chest radiation ( $\geq 20$  Gray) before the age of 30, annual screening MRI and annual screening mammography are covered beginning 8 years after radiation exposure or at age 25, whichever is later.

For women with both a personal history and a family history of breast cancer, annual mammography, annual breast MRI and annual breast ultrasound are covered.

For women with increased breast density, supplemental screening with breast ultrasound, MRI, or digital breast tomosynthesis is not covered.

Breast PET-CT scanning and breast-specific gamma imaging are not covered for breast cancer screening.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

#### DIAGNOSTIC GUIDELINE D7, NEUROIMAGING IN DEMENTIA

Neuroimaging is covered:

- A) To rule out reversible causes of dementia (tumors, normal pressure hydrocephalus and chronic subdural hematoma) via structural neuroimaging only

Neuroimaging is not covered:

- A) For screening of asymptomatic patients for dementia
- B) To predict progression of the risk of developing dementia in patients with mild cognitive impairment
- C) For screening, diagnosis, or monitoring of dementia, with functional neuroimaging (PET, SPECT or fMRI)

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.



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**DIAGNOSTIC GUIDELINE D8, DIAGNOSTIC TESTING FOR OBSTRUCTIVE SLEEP APNEA (OSA) IN ADULTS**

Type I PSG is covered when used to aid the diagnosis of OSA in patients who have clinical signs and symptoms indicative of OSA if performed attended in a sleep lab facility.

OHP clients should have access to least one of the alternatives listed below:

- 1) Type II or Type III sleep testing devices when used to aid the diagnosis of OSA in patients who have clinical signs and symptoms indicative of OSA if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.
- 2) Type IV sleep testing devices measuring three or more channels, one of which is airflow, when used to aid the diagnosis of OSA in patients who have signs and symptoms indicative of OSA if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.
- 3) Sleep testing devices measuring three or more channels that include actigraphy, oximetry, and peripheral arterial tone, when used to aid the diagnosis of OSA in patients who have signs and symptoms indicative of OSA if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.

CPAP titration should be performed as part of the diagnostic study, if possible.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**DIAGNOSTIC GUIDELINE D9, MRI FOR BREAST CANCER DIAGNOSIS**

In women with recently diagnosed breast cancer, preoperative or contralateral MRI of the breast is not a covered service.

**DIAGNOSTIC GUIDELINE D10, MRI IN MULTIPLE SCLEROSIS**

MRI is a diagnostic test for multiple sclerosis and should not be used for routine monitoring of disease.

MRI may be considered in the following circumstances:

- A) Suspected drug failure in the setting of clinical relapse in patients with objective changes in neurological status or documented new clinical symptoms such as urinary urgency or cognitive changes
- B) Evaluation of a clear objective progression in clinical symptoms in patients with previously relapsing disease to rule out ongoing inflammatory disease when conversion to secondary progressive MS is suspected
- C) Patients who require enhanced pharmacovigilance, including
  - 1) Yearly monitoring for patients treated with natalizumab who are JCV seropositive
  - 2) One MRI for patients who switch from natalizumab to other therapeutics (including fingolimod, alemtuzumab and dimethyl fumarate) one year after the switch from natalizumab

**DIAGNOSTIC GUIDELINE D11, MRI OF THE SPINE (CERVICAL AND THORACIC)**

MRI of the cervical and thoracic spine is covered in the following situations:

- 1) Recent onset of major or progressive neurologic deficit (objective evidence of markedly abnormal reflexes, dermatomal muscle weakness, dermatomal sensory loss, EMG or NCV evidence of nerve root impingement), suspected cauda equina syndrome (loss of bowel or bladder control or saddle anesthesia), or neurogenic claudication in patients who are potential candidates for surgery;
- 2) Clinical or radiological suspicion of neoplasm; or,
- 3) Clinical or radiological suspicion of infection.

**DIAGNOSTIC GUIDELINE D12, UPPER ENDOSCOPY FOR GERD OR DYSPEPSIA SYMPTOMS**

Upper endoscopy for uninvestigated dyspepsia or GERD symptoms is covered for:

Patients less than 50 years of age with persistent symptoms following advice on lifestyle modifications and completion of an appropriate course of twice daily PPI therapy or an H. pylori test and treat protocol.

Patients 50 years of age and older

Patients with "alarm symptoms" including, but not limited to, iron deficiency anemia or weight loss

Upper endoscopy is not covered for patients with previous upper endoscopy with non-malignant findings (other than Barrett's esophagus) in the absence of significant new symptoms.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**DIAGNOSTIC GUIDELINE D13, SCREENING FOR CAROTID ARTERY STENOSIS**

Screening for carotid artery stenosis (CPT 93880) in the general primary care population is not a covered service.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**DIAGNOSTIC GUIDELINE D14, LUNG CANCER SCREENING**

Low dose computed tomography is included for annual screening for lung cancer in persons aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a



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**DIAGNOSTIC GUIDELINE D14, LUNG CANCER SCREENING (CONT'D)**

person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. Current smokers should be offered evidence based smoking cessation interventions.

**DIAGNOSTIC GUIDELINE D15, COMPUTER-AIDED MAMMOGRAPHY**

Computer-aided mammography is not intended to be a covered service.

**DIAGNOSTIC GUIDELINE D16, OSTEOPOROSIS SCREENING AND MONITORING IN ADULTS**

Osteoporosis screening by dual-energy X-ray absorptiometry (DXA) is covered only for women aged 65 or older, and for men or younger women whose 10-year risk of major osteoporotic fracture is equal to or greater than 9.3 percent.

Fracture risk should be assessed by the World Health Organization's FRAX tool or similar instrument.

Routine osteoporosis screening by DXA is not covered for men.

The frequency of subsequent monitoring for development of osteoporosis should not be based on DXA scores alone. If rapid change in bone density is expected, more frequent DXA scanning is appropriate (for example, in patients taking glucocorticoids, those with a history of rapid weight loss, those with medical conditions that could result in secondary osteoporosis, etc.).

If there has been no significant change in an individual's risk factors, monitoring by repeat DXA scanning is covered only at the following frequencies:

- once every two years for those with osteoporosis or advanced osteopenia (T-score of -2.00 or lower)
- once every four years for moderate osteopenia (T-score between -1.50 and -1.99)
- once every ten years for mild osteopenia (T-score between -1.01 and -1.49).
- once every fifteen years for those with normal bone density.

Repeat testing is only covered if the results will influence clinical management. For purposes of monitoring osteoporosis medication therapy, testing at intervals of less than two years is not covered.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**DIAGNOSTIC GUIDELINE D17, PRENATAL GENETIC TESTING**

The following types of prenatal genetic testing and genetic counseling are covered for pregnant women:

- A) Genetic counseling (CPT 96040, HPCPS S0265) for high risk women who have family history of inheritable disorder or carrier state, ultrasound abnormality, previous pregnancy with aneuploidy, or elevated risk of neural tube defect.
- B) Genetic counseling (CPT 96040, HPCPS S0265) prior to consideration of chorionic villus sampling (CVS), amniocentesis, microarray testing, Fragile X, and spinal muscular atrophy screening
- C) Validated questionnaire to assess genetic risk in all pregnant women
- D) Screening high risk ethnic groups for hemoglobinopathies (CPT 83020, 83021)
- E) Screening for aneuploidy with any of five screening strategies [first trimester (nuchal translucency, beta-HCG and PAPP-A), integrated, serum integrated, stepwise sequential, and contingency] (CPT 76813, 76814, 81508-81511)
- F) Cell free fetal DNA testing (CPT 81420, 81507) for evaluation of aneuploidy in women who have an elevated risk of a fetus with aneuploidy (maternal age >34, family history or elevated risk based on screening).
- G) Ultrasound for structural anomalies between 18 and 20 weeks gestation (CPT 76811, 76812)
- H) CVS or amniocentesis (CPT 59000, 59015, 82106, 88235, 88267, 88269, 88280, 88285) for a positive aneuploidy screen, maternal age >34, fetal structural anomalies, family history of inheritable chromosomal disorder or elevated risk of neural tube defect.
- I) Array CGH (CPT 81228, 81229) when major fetal congenital anomalies are apparent on imaging, or with normal imaging when array CGH would replace karyotyping performed with CVS or amniocentesis in #8 above.
- J) FISH testing (CPT 88271, 88275) only if karyotyping is not possible due a need for rapid turnaround for reasons of reproductive decision-making (i.e. at 22w4d gestation or beyond)
- K) Screening for Tay-Sachs carrier status (CPT 81255) in high risk populations. First step is hex A, and then additional DNA analysis in individuals with ambiguous Hex A test results, suspected variant form of TSD or suspected pseudodeficiency of Hex A
- L) Screening for cystic fibrosis carrier status once in a lifetime (CPT 81220-81224)
- M) Screening for fragile X status (CPT 81243, 81244) in patients with a personal or family history of
  - a. fragile X tremor/ataxia syndrome
  - b. premature ovarian failure
  - c. unexplained early onset intellectual disability
  - d. fragile X intellectual disability
  - e. unexplained autism through the pregnant woman's maternal line
- N) Screening for spinal muscular atrophy (CPT 81401) once in a lifetime
- O) Screening those with Ashkenazi Jewish heritage for Canavan disease (CPT 81200), familial dysautonomia (CPT 81260), and Tay-Sachs carrier status (CPT 81255). Ashkenazi Jewish carrier panel testing (CPT 81412) is covered if the panel would replace and would be of similar or lower cost than individual gene testing including CF carrier testing.
- P) Expanded carrier screening only for those genetic conditions identified above

The following genetic screening tests are not covered:

3-22-2018 (Includes 1-5-2018 Revisions)

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**DIAGNOSTIC GUIDELINE D17, PRENATAL GENETIC TESTING (CONT'D)**

- A) Serum triple screen
- B) Screening for thrombophilia in the general population or for recurrent pregnancy loss
- C) Expanded carrier screening which includes results for conditions not explicitly recommended for coverage

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**DIAGNOSTIC GUIDELINE D18, ADVANCED IMAGING FOR STAGING OF PROSTATE CANCER**

MRI is covered for men with histologically proven prostate cancer if knowledge of the T or N stage could affect management. CT of the pelvis is covered only when MRI is contraindicated.

Radionuclide bone scanning is not covered in men with low risk localized prostate cancer. Low risk is defined as PSA <10 ng/ml and Gleason score ≤6 and clinical stage T1-T2a.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**DIAGNOSTIC GUIDELINE D19, SPECT**

SPECT (CPT 78451, 78452) is not covered for screening for coronary artery disease in asymptomatic patients.

Stress SPECT (78451, 78452 in conjunction with stress testing) is only covered for diagnosis or risk stratification of coronary artery disease when a stress ECHO is contraindicated, is unavailable or would provide suboptimal imaging (i.e. pre-existing cardiomyopathy, baseline regional wall motion abnormalities, left bundle branch block, paced rhythm, unsuitable acoustic windows due to body habitus, or inability to exercise with inability to utilize dobutamine.)

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**DIAGNOSTIC GUIDELINE D20, OPHTHALMOLOGY DIAGNOSTIC VISITS**

Ophthalmology diagnostic visits (CPT 92002, 92004, 92012, 92014, 92081-92083, 92100, 92140, 92133, 92134) are covered for the evaluation of serious eye symptoms such as sudden vision loss or eye pain.

**DIAGNOSTIC GUIDELINE D21, PHARMACOGENETICS TESTING FOR PSYCHIATRIC MEDICATION MANAGEMENT**

Pharmacogenetics testing for management of psychiatric medications is not a covered service.



# PRACTICE GUIDELINES

GUIDELINE NOTES FOR ANCILLARY AND DIAGNOSTIC SERVICES  
NOT APPEARING ON THE JANUARY 1, 2018 PRIORITIZED LIST  
OF HEALTH SERVICES

GUIDELINE NOTES FOR HEALTH SERVICES  
THAT APPEAR ON THE JANUARY 1, 2018 PRIORITIZED LIST  
OF HEALTH SERVICES



**GUIDELINE NOTE 1, ROUTINE CERVICAL CANCER SCREENING***Line 3*

Cervical cancer screening is covered on Line 3 for women:

Age group in years	Type of screening covered	Frequency
<21	None	Never
21-29	Cytology alone Mandatory HPV testing (87620-87621) is not covered for women age 21-29	Every 3 years
30-65	Co-testing* or cytology alone	Co-testing every 5 years Cytology alone every 3 years
>65	None Unless adequate screening** has not been achieved, or it is <20 years after regression or appropriate management of a high-grade precancerous lesion	Never
Women who have had a hysterectomy with removal of cervix for non cervical cancer related reasons (i.e. other than high grade precancerous lesion, CIN 2 or 3, or cervical cancer)	None	Never
Women who have abnormal testing	Per ASCCP*** Guideline, until indicated to resume routine screening	Per ASCCP Guideline, until indicated to resume routine screening

\*Co-testing is defined as simultaneous cytology and mandatory HPV testing.

\*\* Adequate screening is defined as 3 consecutive negative cytology results or 2 consecutive negative HPV results within 10 years of the cessation of screening, with the most recent test occurring within 5 years.

\*\*\* American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology guideline (Saslow 2012)

Women who have received a diagnosis of a high-grade precancerous cervical lesion or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who are immunocompromised (such as those who are HIV positive) are intended to have screening more frequently than delineated in this guideline.

The development of this guideline note was informed by a HERC [coverage guidance](#). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 2, FETOSCOPIC SURGERY***Line 1*

Fetal surgery is only covered for the following conditions: repair of urinary tract obstructions via placement of a urethral shunt, repair of congenital cystic adenomatoid malformation, repair of extralobal pulmonary sequestration, repair of sacrococcygeal teratoma, and therapy for twin-twin transfusion syndrome.

Fetoscopic repair of urinary tract obstruction (S2401) is only covered for placement of a urethral shunt. Fetal surgery for cystic adenomatoid malformation of the lung, extralobal pulmonary sequestration and sacrococcygeal teratoma must show evidence of developing hydrops fetalis.

Certification of laboratory required (76813-76814).

**GUIDELINE NOTE 3, PROPHYLACTIC TREATMENT FOR PREVENTION OF BREAST CANCER IN HIGH RISK WOMEN***Line 191*

Bilateral prophylactic breast removal and/or oophorectomy are included on Line 191 for women without a personal history of invasive breast cancer who meet the criteria in the NCCN Clinical Practice Guidelines in Oncology. Breast Cancer Risk Reduction. V.1.2016 (2/23/16). [www.nccn.org](http://www.nccn.org). Prior to surgery, women without a personal history of breast cancer must have a genetics consultation as defined in section A2 of the DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE.

Contralateral prophylactic mastectomy is included on Line 191 for women with a personal history of breast cancer.

**GUIDELINE NOTE 4, TOBACCO DEPENDENCE, INCLUDING DURING PREGNANCY***Lines 1,5*

Pharmacotherapy (including varenicline, bupropion and all five FDA-approved forms of nicotine-replacement therapy) and behavioral counseling are included on this line, alone or in combination, for at least two quit attempts per year. At least two quit attempts per year



#### GUIDELINE NOTE 4, TOBACCO DEPENDENCE, INCLUDING DURING PREGNANCY (CONT'D)

must be provided without prior authorization, and each attempt can include both pharmacotherapy and behavioral counseling. Combination drug therapy (i.e. two forms of NRT or NRT plus bupropion) is also included with each quit attempt without prior authorization. However, nicotine inhalers and sprays may be subject to prior authorization.

A minimum of four counseling sessions of at least 10 minutes each (group or individual, telephonic or in person) are included for each quit attempt. More intensive interventions and group therapy are likely to be the most effective behavioral interventions. During pregnancy, additional intensive behavioral counseling is strongly encouraged. All tobacco cessation interventions during pregnancy are not subject to quantity or duration limits.

Inclusion on this line follows the minimum standard criteria as defined in the Oregon Public Health Division "Standard Tobacco Cessation Coverage" (based on the Patient Protection and Affordable Care Act), available here:

[http://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/TOBACCO/TOBACCO/DOCUMENTS/tob\\_cessation\\_coverage\\_standards.pdf](http://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/TOBACCO/TOBACCO/DOCUMENTS/tob_cessation_coverage_standards.pdf). The USPSTF has also made "A" recommendations for screening, counseling, and treatment of pregnant and nonpregnant adults, included in Guideline Note 106.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

#### GUIDELINE NOTE 5, OBESITY AND OVERWEIGHT

*Line 320*

Medical treatment of overweight (with known cardiovascular risk factors) and obesity in adults is limited to intensive counseling on nutrition and physical activity, provided by health care professionals. Intensive counseling is defined as face-to-face contact more than monthly. A multidisciplinary team is preferred, but a single clinician could also deliver intensive counseling in primary care or other settings.

Intensive counseling visits are included on this line for 6 months. Intensive counseling visits may continue for an additional 6 months (up to 12 months) as long as there is evidence of continued weight loss or improvement in cardiovascular risk factors based on the intervention. Maintenance visits at the conclusion of the intensive treatment are included on this line no more than monthly after this intensive counseling period. The characteristics of effective behavioral interventions include: high intensity programs; multicomponent (including at a minimum diet and exercise), group-based commercial programs; Mediterranean diet; and the following sub-elements -- calorie counting, contact with a dietician, and comparison to peers.

Known cardiovascular risk factors in overweight persons for which this therapy is effective include: hypertension, dyslipidemia, prediabetes, or the metabolic syndrome.

Medical treatment of obesity in children is limited to comprehensive, intensive behavioral interventions. For treatment of children up to 12 years old, interventions may be targeted only to parents, or to both parents and children.

Pharmacological treatments and devices (e.g. gastric balloons, duodenal jejunal bypass liners, and vagus nerve blocking devices) for obesity are not intended to be included as services on this line or any other line on the Prioritized List.

#### GUIDELINE NOTE 6, REHABILITATIVE AND HABILITATIVE THERAPIES

*Lines 31,46,57,68,71,72,74,81,91,92,131,132,136,150,153,160,178,183,184,196,197,201,202,208,255,257,272,285,287,292,300,301,309,317,341,345,348,355,356,359,376,377,400,407,415,417,421,422,430,441,453,461,464,465,476,484,495,507,553,556,569,586,605*

The quantitative limits in this guideline note do not apply to mental health or substance abuse conditions.

A total of 30 visits per year of rehabilitative therapy and a total of 30 visits per year of habilitative therapy (physical, occupational and speech therapy) are included on these lines when medically appropriate. Additional visits, not to exceed 30 visits per year of rehabilitative therapy and 30 visits per year of habilitative therapy, may be authorized in cases of a new acute injury, surgery, or other significant change in functional status. Children under age 21 may have additional visits authorized beyond these limits if medically appropriate.

Physical, occupational and speech therapy are only included on these lines when the following criteria are met:

- A) therapy is provided by a licensed physical therapist, occupational therapist, speech language pathologist, physician, or other practitioner licensed to provide the therapy,
- B) there is objective, measurable documentation of clinically significant progress toward the therapy plan of care goals and objectives,
- C) the therapy plan of care requires the skills of a medical provider, and
- D) the client and/or caregiver cannot be taught to carry out the therapy regimen independently.

No limits apply while in a skilled nursing facility for the primary purpose of rehabilitation, an inpatient hospital or an inpatient rehabilitation unit.

Spinal cord injuries, traumatic brain injuries, or cerebral vascular accidents are not subject to the visit limitations during the first year after an acute injury.



**GUIDELINE NOTE 7, ERYTHROPOIESIS-STIMULATING AGENT (ESA) GUIDELINE**

Lines 12,59,93,95,112-116,126,133,135,157,158,161,163,179,191,200,201,209,211,215,216,218,230,235,238,239,259-263,271,276,286-288,294,295,314-316,329,396,397,400,418,433,556,589

- A) Indicated for anemia (Hgb < 10gm/dl or Hct < 30%) induced by cancer chemotherapy given within the previous 8 weeks or in the setting of myelodysplasia.
  - 1) Reassessment should be made after 8 weeks of treatment. If no response, treatment should be discontinued. If response is demonstrated, ESAs should be discontinued once the hemoglobin level reaches 10, unless a lower hemoglobin level is sufficient to avoid the need for red blood cell (RBC) transfusion.
- B) Indicated for anemia (Hgb < 10gm/dl or HCT < 30%) associated with HIV/AIDS.
  - 1) An endogenous erythropoietin level < 500 IU/L is required for treatment, and patient may not be receiving zidovudine (AZT) > 4200 mg/week.
  - 2) Reassessment should be made after 8 weeks. If no response, treatment should be discontinued. If response is demonstrated, the lowest ESA dose sufficient to reduce the need for RBC transfusions should be used, and the Hgb should not exceed 11gm/dl.
- C) Indicated for anemia (Hgb < 10 gm/dl or HCT <30%) associated with chronic renal failure, with or without dialysis.
  - 1) Reassessment should be made after 12 weeks. If no response, treatment should be discontinued. If response is demonstrated, the lowest ESA dose sufficient to reduce the need for RBC transfusions should be used, and the Hgb should not exceed 11gm/dl. In those not on dialysis, the Hgb level should not exceed 10gm/dl.

**GUIDELINE NOTE 8, BARIATRIC SURGERY**

Line 320

Bariatric/metabolic surgery (limited to Roux-en-Y gastric bypass, and sleeve gastrectomy) is included on Line 320 when the following criteria are met:

- A) Age ≥ 18
- B) The patient has obesity with a:
  - 1) BMI ≥ 40 OR
  - 2) BMI ≥ 35 with:
    - a) Type 2 diabetes, OR
    - b) at least two of the following other serious obesity-related comorbidities: hypertension, coronary heart disease, mechanical arthropathy in major weight bearing joint, sleep apnea
- C) Repeat bariatric surgery is included when it is a conversion from a less intensive (such as gastric band or sleeve gastrectomy) to a more intensive surgery (e.g. Roux-en-Y). Repair of surgical complications (excluding failure to lose sufficient weight) are also included on this and other lines. Reversal of surgical procedures and devices is included on this line when benefits of reversal outweigh harms.
- D) Participate in the following four evaluations and meet criteria as described.
  - 1) Psychosocial evaluation: (Conducted by a licensed mental health professional)
    - a) Evaluation to assess potential compliance with post-operative requirements.
    - b) Must remain free of abuse of or dependence on alcohol during the six-month period immediately preceding surgery. No current use of any nicotine product or illicit drugs and must remain abstinent from their use during the six-month observation period. Testing will, at a minimum, be conducted within 1 month of the quit date and within 1 month of the surgery to confirm abstinence from illicit drugs. Tobacco and nicotine abstinence to be confirmed in active users by negative cotinine levels at least 6 months apart, with the second test within one month of the surgery date.
    - c) No mental or behavioral disorder that may interfere with postoperative outcomes<sup>1</sup>.
    - d) Patient with psychiatric illness must be stable for at least 6 months.
  - 2) Medical evaluation: (Conducted by OHP primary care provider)
    - a) Pre-operative physical condition and mortality risk assessed with patient found to be an appropriate candidate.
    - b) Optimize medical control of diabetes, hypertension, or other co-morbid conditions.
    - c) Female patient not currently pregnant with no plans for pregnancy for at least 2 years post-surgery. Contraception methods reviewed with patient agreement to use effective contraception through 2nd year post-surgery.
  - 3) Surgical evaluation: (Conducted by a licensed bariatric surgeon associated with program<sup>2</sup>)
    - a) Patient found to be an appropriate candidate for surgery at initial evaluation and throughout period leading to surgery.
    - b) Received counseling by a credentialed expert on the team regarding the risks and benefits of the procedure and understands the many potential complications of the surgery (including death) and the realistic expectations of post-surgical outcomes.
  - 4) Dietician evaluation: (Conducted by licensed dietician)
    - a) Evaluation of adequacy of prior dietary efforts to lose weight. If no or inadequate prior dietary effort to lose weight, must undergo six-month clinically supervised weight reduction program (including intensive nutrition and physical activity counseling as defined by the USPSTF).
    - b) Counseling in dietary lifestyle changes
- E) Participate in additional evaluations:
  - 1) Post-surgical attention to lifestyle, an exercise program and dietary changes and understands the need for post-surgical follow-up with all applicable professionals (e.g. nutritionist, psychologist/psychiatrist, exercise physiologist or physical therapist, support group participation, regularly scheduled physician follow-up visits).

<sup>1</sup> Many patients (>50%) have depression as a co-morbid diagnosis that, if treated, would not preclude their participation in the bariatric surgery program.



**GUIDELINE NOTE 8, BARIATRIC SURGERY (CONT'D)**

<sup>2</sup> All surgical services must be provided by a program with current accreditation (as a comprehensive center or low acuity center) by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP)

**GUIDELINE NOTE 9, WIRELESS CAPSULE ENDOSCOPY**

*Lines 29,56*

- A) Wireless capsule endoscopy is included on these lines for diagnosis of:
  - 1) Obscure GI bleeding suspected to be of small bowel origin with iron deficiency anemia or documented GI blood loss
  - 2) Suspected Crohn's disease with prior negative work up
- B) Wireless capsule endoscopy is not included on these lines for:
  - 1) Colorectal cancer screening
  - 2) Confirmation of lesions of pathology normally within the reach of upper or lower endoscopes (lesions proximal to the ligament of Treitz or distal to the ileum)
- C) Wireless capsule endoscopy is only included on these lines when the following conditions have been met:
  - 1) Prior studies must have been performed and been non-diagnostic
    - a) GI bleeding: upper and lower endoscopy
    - b) Suspected Crohn's disease: upper and lower endoscopy, small bowel follow through
  - 2) Radiological evidence of lack of stricture
  - 3) Only covered once during any episode of illness
  - 4) FDA approved devices must be used
  - 5) Patency capsule should not be used prior to procedure

**GUIDELINE NOTE 10, CENTRAL SEROUS CHORIORETINOPATHY AND POSTERIOR CYCLITIS**

*Lines 360,383*

Central serous chorioretinopathy (ICD-10-CM H35.71) is included on Line 383 only for treatment when the condition has been present for three months or longer. Posterior Cyclitis (ICD-10-CM H30.2) should only be treated in patients with 20/40 or worse vision.

**GUIDELINE NOTE 11, COLONY STIMULATING FACTOR (CSF) GUIDELINES**

*Lines 93,95,112-116,126,133,135,157,158,161,163,179,191,200,201,209,211,215,216,218,230,235,238,239,259-263,271,276,286-288,294,314-316,329,396,397,400,418,433,556,589*

- A) CSF are not indicated for primary prophylaxis of febrile neutropenia unless the primary chemotherapeutic regimen is known to produce febrile neutropenia at least 20% of the time. CSF should be considered when the primary chemotherapeutic regimen is known to produce febrile neutropenia 10-20% of the time; however, if the risk is due to the chemotherapy regimen, other alternatives such as the use of less myelosuppressive chemotherapy or dose reduction should be explored in this situation.
- B) For secondary prophylaxis, dose reduction should be considered the primary therapeutic option after an episode of severe or febrile neutropenia except in the setting of curable tumors (e.g., germ cell), as no disease free or overall survival benefits have been documented using dose maintenance and CSF.
- C) CSF are not indicated in patients who are acutely neutropenic but afebrile.
- D) CSF are not indicated in the treatment of febrile neutropenia except in patients who received prophylactic filgrastim or sargramostim or in high risk patients who did not receive prophylactic CSF. High risk patients include those age >65 years or with sepsis, severe neutropenia with absolute neutrophil count <100/mcl, neutropenia expected to be more than 10 days in duration, pneumonia, invasive fungal infection, other clinically documented infections, hospitalization at time of fever, or prior episode of febrile neutropenia.
- E) CSF are not indicated to increase chemotherapy dose-intensity or schedule, except in cases where improved outcome from such increased intensity has been documented in a clinical trial.
- F) CSF (other than pegfilgrastim) are indicated in the setting of autologous progenitor cell transplantation, to mobilize peripheral blood progenitor cells, and after their infusion.
- G) CSF are NOT indicated in patients receiving concomitant chemotherapy and radiation therapy.
- H) There is no evidence of clinical benefit in the routine, continuous use of CSF in myelodysplastic syndromes. CSF may be indicated for some patients with severe neutropenia and recurrent infections, but should be used only if significant response is documented.
- I) CSF is indicated for treatment of cyclic, congenital and idiopathic neutropenia.

**GUIDELINE NOTE 12, TREATMENT OF CANCER WITH LITTLE OR NO BENEFIT**

*Lines 93,112-116,125,129,133,135,157,158,163,179,191,200,201,209,211,215,216,218,230,235,238,239,259-263,271,276,286,287,294,314-316,329,372,396,397,418,433,589,600*

Cancer is a complex group of diseases with treatments that vary depending on the specific subtype of cancer and the patient's unique medical and social situation. Goals of appropriate cancer therapy can vary from intent to cure, disease burden reduction, disease stabilization and control of symptoms. Cancer care must always take place in the context of the patient's support systems, overall health, and core values. Patients should have access to appropriate peer-reviewed clinical trials of cancer therapies. A comprehensive multidisciplinary approach to treatment should be offered including palliative care services (see STATEMENT OF INTENT 1, PALLIATIVE CARE).

Treatment with intent to prolong survival is not a covered service for patients who have progressive metastatic cancer with



**GUIDELINE NOTE 12, TREATMENT OF CANCER WITH LITTLE OR NO BENEFIT (CONT'D)**

- A) Severe co-morbidities unrelated to the cancer that result in significant impairment in two or more major organ systems which would affect efficacy and/or toxicity of therapy; OR
- B) A continued decline in spite of best available therapy with a non reversible Karnofsky Performance Status or Palliative Performance score of <50% with ECOG performance status of 3 or higher which are not due to a pre-existing disability.

Treatments with intent to relieve symptoms or improve quality of life are covered as defined in STATEMENT OF INTENT 1, PALLIATIVE CARE.

Examples include:

- A) Single-dose radiation therapy for painful bone metastases with the intent to relieve pain and improve quality of life.
- B) Surgical decompression for malignant bowel obstruction.
- C) Medication therapy such as chemotherapy with low toxicity/low side effect agents with the goal to decrease pain from bulky disease or other identified complications. Cost of chemotherapy and alternative medication(s) should also be considered.

To qualify for treatment coverage, the cancer patient must have a documented discussion about treatment goals, treatment prognosis and the side effects, and knowledge of the realistic expectations of treatment efficacy. This discussion may take place with the patient's oncologist, primary care provider, or other health care provider, but preferably in a collaborative interdisciplinary care coordination discussion. Treatment must be provided via evidence-driven pathways (such as NCCN, ASCO, ASH, ASBMT, or NIH Guidelines) when available.

**GUIDELINE NOTE 13, HEMANGIOMAS, COMPLICATED**

*Lines 321,625*

Dermatologic hemangiomas (ICD-10-CM D18.01 Hemangioma and Lymphangioma of skin and subcutaneous tissue) are included on Line 321 when they are ulcerated, infected, recurrently hemorrhaging, or function-threatening (e.g. eyelid hemangioma). Otherwise, they are included on Line 625.

**GUIDELINE NOTE 14, SECOND BONE MARROW TRANSPLANTS**

*Lines 95,114,116,130,163,179,218,261,288*

Second bone marrow transplants are not covered except for tandem autologous transplants for multiple myeloma.

**GUIDELINE NOTE 15, HETEROTOPIC BONE FORMATION**

*Lines 81,356*

Radiation treatment is indicated only in those at high risk of heterotopic bone formation: those with a history of prior heterotopic bone formation, ankylosing spondylitis or hypertrophic osteoarthritis.

**GUIDELINE NOTE 16, PROTON BEAM THERAPY FOR CANCER**

*Lines 93,113,126,129,191,201,238,276,287,294,372,396,397*

Proton beam therapy is included on Lines 113 CANCER OF EYE AND ORBIT, 126 BENIGN NEOPLASM OF THE BRAIN AND SPINAL CORD and 294 CANCER OF BRAIN AND NERVOUS SYSTEM.

Proton beam therapy is included on Lines 129, 201 and 287 only for: malignant skull base, paranasal sinus (including lethal midline granuloma), spinal, and juxtaspinal tumors .

Proton beam therapy is additionally included on Lines 93, 191, 238, 276, 396 and 397 only for pediatric malignant tumors (incident cancer under age 21.)

**GUIDELINE NOTE 17, PREVENTIVE DENTAL CARE**

*Lines 3,53*

Dental cleaning is limited to once per 12 months for adults and twice per 12 months for children up to age 19 (D1110, D1120). More frequent dental cleanings may be required for certain higher risk populations.

Fluoride varnish (99188) is included on Line 3 for use with children 18 and younger during well child preventive care visits. Fluoride treatments (D1206 and D1208) are included on Line 53 PREVENTIVE DENTAL SERVICES for use with adults and children during dental visits. The total number of fluoride applications provided in all settings is not to exceed four per twelve months for a child at high risk for dental caries and two per twelve months for a child not at high risk. The number of fluoride treatments is limited to once per 12 months for average risk adults and up to four times per 12 months for high risk adults.



**GUIDELINE NOTE 18, VENTRICULAR ASSIST DEVICES**

*Lines 82,98,264*

Ventricular assist devices are covered as a bridge to cardiac transplant; as treatment for pulmonary hypertension when pulmonary hypertension is the only contraindication to cardiac transplant and the anticipated outcome is cardiac transplant; as a bridge to recovery; or as destination therapy.

When used as destination therapy, patients must

- A) have chronic end-stage heart failure (New York Heart Association Class IIIB or IV end-stage left ventricular failure) for more than 60 days, AND
- B) not be a candidate for heart transplantation, AND
- C) meet all of the following conditions:
  - 1) Have failed to respond to optimal medical management, including beta-blockers and ACE inhibitors (if tolerated) for at least 45 of the last 60 days, or have been balloon pump dependent for 7 days, or IV inotrope dependent for 14 days; and
  - 2) Have a left ventricular ejection fraction (LVEF) <25%; and
  - 3) Have demonstrated functional limitation with a peak oxygen consumption of <14 ml/kg/min unless balloon pump or inotrope dependent or physically unable to perform the test.
- D) Have adequate psychological condition and appropriate external psychosocial support for prolonged VAD support
- E) Have adequate end organ function

**GUIDELINE NOTE 19, PET SCAN GUIDELINES**

*Lines 113,116,133,135,157,158,163,174,200,201,211,230,260,263,276,287,314*

PET Scans are covered for diagnosis of the following cancers only:

- Solitary pulmonary nodules and non-small cell lung cancer
- Evaluation of cervical lymph node metastases when CT or MRI do not demonstrate an obvious primary tumor.

For diagnosis, PET is covered only when it will avoid an invasive diagnostic procedure, or will assist in determining the optimal anatomic location to perform an invasive diagnostic procedure.

PET scans are covered for the initial staging of the following cancers:

- Cervical cancer only when initial MRI or CT is negative for extra-pelvic metastasis
- Head and neck cancer when initial MRI or CT is equivocal
- Colon cancer
- Esophageal cancer
- Solitary pulmonary nodule
- Non-small cell lung cancer
- Lymphoma
- Melanoma

For staging, PET is covered when clinical management of the patient will differ depending on the stage of the cancer identified and either:

- A) the stage of the cancer remains in doubt after standard diagnostic work up, OR
- B) PET replaces one or more conventional imaging studies when they are insufficient for clinical management of the patient.

Restaging is covered only for cancers for which staging is covered and for thyroid cancer if recurrence is suspected and I131 scintigraphy is negative. For restaging, PET is covered after completion of treatment for the purpose of detecting residual disease, for detecting suspected recurrence or to determine the extent of a known recurrence. PET is not covered to monitor tumor response during the planned course of therapy. PET scans are NOT indicated for routine follow up of cancer treatment or routine surveillance in asymptomatic patients.

PET scans are also indicated for preoperative evaluation of the brain in patients who have intractable seizures and are candidates for focal surgery. PET scans are NOT indicated for cardiac evaluation.

**GUIDELINE NOTE 20, ATTENTION DEFICIT/HYPERACTIVITY DISORDERS IN CHILDREN**

*Line 122*

Use of ICD-10-CM F90.9, Attention deficit/hyperactivity disorder, unspecified type, in children age 5 and under, is appropriate only when the following apply:

- Child does not meet the full criteria for the full diagnosis because of their age.
- For children age 3 and under, when the child exhibits functional impairment due to hyperactivity that is clearly in excess of the normal activity range for age (confirmed by the evaluating clinician's observation, not only the parent/caregiver report), and when the child is very limited in his/her ability to have the sustained periods of calm, focused activity which would be expected for the child's age.

For children age 5 and under diagnosed with disruptive behavior disorders, including those at risk for ADHD, first line therapy is evidence-based, structured "parent-behavior training. Second line therapy is pharmacotherapy.



**GUIDELINE NOTE 20, ATTENTION DEFICIT/HYPERACTIVITY DISORDERS IN CHILDREN (CONT'D)**

For children age 6 and over who are diagnosed with ADHD, pharmacotherapy alone or pharmacotherapy with psychosocial/behavioral treatment are included on this line for first line therapy.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 21, SEVERE INFLAMMATORY SKIN DISEASE**

*Lines 424,480,502,530,539,654*

Inflammatory skin conditions included in this guideline are:

- A) Psoriasis
- B) Atopic dermatitis
- C) Lichen planus
- D) Darier disease
- E) Pityriasis rubra pilaris
- F) Discoid lupus

The conditions above are included on line 424 if severe, defined as having functional impairment (e.g. inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) AND one or more of the following:

- A) At least 10% of body surface area involved
- B) Hand, foot or mucous membrane involvement.

Otherwise, these conditions above are included on Lines 480, 502, 530, 539 and 654.

For severe psoriasis, first line agents include topical agents, phototherapy and methotrexate. Second line agents include other systemic agents and oral retinoids and should be limited to those who fail, or have contraindications to, or do not have access to first line agents. Biologics are included on this line only for the indication of severe plaque psoriasis; after documented failure of first line agents and failure of (or contraindications to) a second line agent.

For severe atopic dermatitis/eczema, first line agents include topical corticosteroids, narrowband UVB, cyclosporine, methotrexate, and azathioprine. Second line agents include topical pimecrolimus and topical tacrolimus and should be limited to those who fail or have contraindications to first line agents. Biologic agents are included on this line for atopic dermatitis only after failure of or contraindications to first and second line agents.

**GUIDELINE NOTE 22, PLANNED CESAREAN DELIVERY**

*Line 1*

Cesarean delivery on maternal request without medical or obstetrical indication is not included on this line (or the list). Planned cesarean delivery is also not included on this line (or the list) for: small for gestational age; suspected cephalopelvic disproportion; maternal Hepatitis B infection; or maternal Hepatitis C infection.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 23, COLON CANCER SURVEILLANCE**

*Line 157*

- A) History and physical exam is indicated every 3 to 6 months for the first three years after primary therapy, then annually thereafter.
- B) CEA testing should be performed every 2-3 months after colon resection for at least two years in patients with stage II or III disease for whom resection of liver metastases is clinically indicated
- C) Colonoscopy is indicated every 3 to 5 years.
- D) No other surveillance testing is indicated.

**GUIDELINE NOTE 24, COMPLICATED HERNIAS**

*Lines 168,522*

Complicated hernias are included on Line 168 if they cause symptoms of intestinal obstruction and/or strangulation. Incarcerated hernias (defined as non-reducible by physical manipulation) are also included on Line 168, excluding incarcerated ventral hernias. Incarcerated ventral hernias are included on Line 522, because the chronic incarceration of large ventral hernias does not place the patient at risk for impending strangulation.

**GUIDELINE NOTE 25, STEM CELL TRANSPLANTATION FOR NEUROBLASTOMA**

*Line 260*

Stem cell transplantation (CPT 38204-38215, 38230-38241) is only included on this line for treatment of high risk neuroblastoma (ICD-10-CM C74).



**GUIDELINE NOTE 26, BREAST CANCER SURVEILLANCE**

*Line 191*

- A) History and physical exam is indicated every 3 to 6 months for the first three years after primary therapy, then every 6-12 months for the next 2 years, then annually thereafter.
- B) Mammography is indicated annually, and patients treated with breast conserving therapy, initial mammogram of the affected breast should be 6 months after completion of radiotherapy.
- C) No other surveillance testing is indicated.

**GUIDELINE NOTE 27, SLEEP APNEA**

*Line 203*

CPAP is covered initially when all of the following conditions are met:

- 12 week 'trial' period to determine benefit. This period is covered if apnea-hypopnea index (AHI) or respiratory disturbance index (RDI) is greater than or equal to 15 events per hour; or if between 5 and 14 events with additional symptoms including one or more of the following:
  - excessive daytime sleepiness defined as either an Epworth Sleepiness Scale score >10 or daytime sleepiness interfering with ADLs that is not attributable to another modifiable sedating condition (e.g. narcotic dependence), or
  - documented hypertension, or
  - ischemic heart disease, or
  - history of stroke;
- Providers must provide education to patients and caregivers prior to use of CPAP machine to ensure proper use; and
- Positive diagnosis through polysomnogram (PSG) or Home Sleep Test (HST).

CPAP coverage subsequent to the initial 12 weeks is based on documented patient tolerance, compliance, and clinical benefit. Compliance (adherence to therapy) is defined as use of CPAP for at least four hours per night on 70% of the nights during a consecutive 30-day period.

Mandibular advancement devices (oral appliances) are covered for those for whom CPAP fails or is contraindicated.

Surgery for sleep apnea in adults is not included on this line (due to lack of evidence of efficacy). Surgical codes are included on this line only for children who meet criteria according to Guideline Note 118 OBSTRUCTIVE SLEEP APNEA DIAGNOSIS AND TREATMENT FOR CHILDREN.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 28, TROCHANTERIC BURSITIS**

*Lines 376,503*

Trochanteric bursitis (ICD-10-CM M70.6 and M70.7) is included on Line 376 for pairing with physical therapy and steroid joint injections. Trochanteric bursitis is included on Line 503 for pairing with surgical interventions (i.e. CPT 27062).

**GUIDELINE NOTE 29, TYMPANOSTOMY TUBES IN ACUTE OTITIS MEDIA**

*Line 389*

Tympanostomy tubes (CPT 69436) are only included on this line as treatment for:

- A) recurrent acute otitis media (three or more well-documented and separate episodes in six months or four or more well-documented and separate episodes in the past 12 months with at least one episode in the past six months) in patients who have unilateral or bilateral middle ear effusion at the time of assessment for tube candidacy, or
- B) patients with complicating conditions (immunocompromised host, meningitis by lumbar puncture, acute mastoiditis, sigmoid sinus/jugular vein thrombosis by CT/MRI/MRA, cranial nerve paralysis, sudden onset dizziness/vertigo, need for middle ear culture, labyrinthitis, or brain abscess).

Patients with craniofacial anomalies, Down's syndrome, cleft palate, permanent hearing loss of 25dB or greater independent of otitis media with effusion, and patients with speech and language delay may be considered for tympanostomy if unresponsive to appropriate medical treatment or having recurring infections (without needing to meet the strict "recurrent" definition above).

Removal of retained tympanostomy tubes requiring anesthesia (CPT code 69424) or as an office visit, is included on Line 422 as a complication, pairing with ICD-10-CM H74.8.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.



**GUIDELINE NOTE 30, TESTICULAR CANCER**

*Line 218*

The treatment of testicular cancer with bone marrow/stem cell rescue and transplant in conjunction with high-dose chemotherapy is included only after multiple (at least 2) recurrences after standard chemotherapy.

**GUIDELINE NOTE 31, COCHLEAR IMPLANTATION**

*Line 326*

Patients will be considered candidates for cochlear implants if the following criteria are met:

- A) Severe to profound sensorineural hearing loss in both ears (defined as 71dB hearing loss or greater at 500, 1000 and 2000 Hz)
- B) Receive limited useful benefit from appropriately fitted hearing aids, defined as a speech discrimination score of <30% on age appropriate testing for children and as scores of 40% or less on sentence recognition test in the best-aided listening condition for adults
- C) No medical contraindications
- D) High motivation and appropriate expectations (both patient and family, when appropriate)

Bilateral cochlear implants are included on this line. Simultaneous implantation appears to be more cost-effective than sequential implantation.

**GUIDELINE NOTE 32, CATARACT**

*Line 296*

Cataract extraction is covered for binocular visual acuity of 20/50 or worse OR monocular visual acuity of 20/50 or worse with the recent development of symptoms related to poor vision that affect activities of daily living (ADLs). Cataract removal must be likely to restore vision and allow the patient to resume activities of daily living. There are rare instances where cataract removal is medically necessary even if visual improvement is not the primary goal:

- A) Hypermature cataract causing inflammation and glaucoma OR
- B) To see the back of the eye to treat posterior segment conditions that could not be monitored due to the poor view and very dense lens opacity (i.e. diabetic retinopathy, glaucoma) OR
- C) Significant anisometropia causing aniseikonia.

**GUIDELINE NOTE 33, NITROUS OXIDE FOR LABOR PAIN**

*Line 1*

Nitrous oxide for labor pain is included on this line.

**GUIDELINE NOTE 34, EXTRACTION OF IMPACTED WISDOM TEETH**

*Line 344*

Extraction of impacted wisdom teeth (D7220, D7230, D7240, D7241, D7250) is only included on this line when there is

- A) Evidence of pathology. Such pathology includes unresorable caries, non-treatable pulpal and/or periapical pathology, cellulitis, abscess and osteomyelitis, internal/external resorption of the tooth or adjacent teeth, fracture of tooth, disease of follicle including cyst/tumour, tooth/teeth impeding surgery or reconstructive jaw surgery, and when a tooth is involved in or within the field of tumour resection OR
- B) Two or more episodes of pericoronitis OR
- C) Severe pain directly related to the impacted tooth that does not respond to conservative treatment. (Extraction for pain or discomfort related to normal tooth eruption or for non-specific symptoms such as "headaches" or "jaw pain" is not considered medically or dentally necessary for treatment.)

**GUIDELINE NOTE 35, SINUS SURGERY**

*Lines 287,463,504*

Sinus surgery (other than adenoidectomy) is indicated when at least one of the following circumstances occur (A-G):

- A) Recurrent acute rhinosinusitis, defined as 4 or more episodes of acute bacterial rhinosinusitis in one year without signs or symptoms of rhinosinusitis between episodes and have failed optimal medical management defined as nasal steroid therapy and nasal saline therapy, in patients who are compliant with oral antibiotics and/or oral corticosteroids for management of acute episodes of rhinosinusitis

OR

- B) Chronic sinusitis defined as 12 weeks of continuous symptoms without improvement with one of the following (1-3):
  - 1) Findings of obstruction of active infection on CT scan OR
  - 2) Symptomatic mucocele OR
  - 3) Negative CT scan but significant disease found on nasal endoscopy

AND



**GUIDELINE NOTE 35, SINUS SURGERY (CONT'D)**

Failure of medical therapy defined as (1-2)

4) Two or more courses of antibiotics with adequate doses AND

5) Trial of inhaled and/or oral steroids (2 or more courses of adequate doses of one or both)

OR

C) Nasal polyposis causing or contributing to sinusitis

OR

D) Complications of sinusitis including subperiosteal or orbital abscess, Pott's puffy tumor, brain abscess or meningitis

OR

E) Invasive or allergic fungal sinusitis

OR

F) Tumor of nasal cavity or sinuses

OR

G) CSF rhinorrhea

Adenoidectomy (CPT 42830, 42835) is included on Line 463 only for treatment of children with chronic sinusitis who fail appropriate medical therapy.

**GUIDELINE NOTE 36, ADENOTONSILLECTOMY FOR INDICATIONS OTHER THAN OBSTRUCTIVE SLEEP APNEA**

*Lines 42,47,368,548*

Tonsillectomy/adentonsillectomy is an appropriate treatment for patients with:

- A) Five documented attacks of strep tonsillitis in a year or 3 documented attacks of strep tonsillitis in each of two consecutive years where an attack is considered a positive culture/screen and where an appropriate course of antibiotic therapy has been completed;
- B) Peritonsillar abscess requiring surgical drainage; or,
- C) Unilateral tonsillar hypertrophy in adults; unilateral tonsillar hypertrophy in children with other symptoms suggestive of malignancy.

ICD-10-CM J35.1 and J35.3 are included on Line 368 only for 1) unilateral tonsillar hypertrophy in adults and 2) unilateral tonsillar hypertrophy in children with other symptoms suggestive of malignancy. Bilateral tonsillar hypertrophy and unilateral tonsillar hypertrophy in children without other symptoms suggestive of malignancy are included only on Line 548.

See Guideline Note 118 for diagnosis and treatment of obstructive sleep apnea in children.

**GUIDELINE NOTE 37, SURGICAL INTERVENTIONS FOR CONDITIONS OF THE BACK AND SPINE OTHER THAN SCOLIOSIS**

*Lines 346,527*

Spine surgery is included on Line 346 only in the following circumstances:

- A) Decompressive surgery is included on Line 346 to treat debilitating symptoms due to central or foraminal spinal stenosis, and only when the patient meets the following criteria:
  - 1) Has MRI evidence of moderate or severe central or foraminal spinal stenosis AND
  - 2) Has neurogenic claudication OR
  - 3) Has objective neurologic impairment consistent with the MRI findings. Neurologic impairment is defined as objective evidence of one or more of the following:
    - a) Markedly abnormal reflexes
    - b) Segmental muscle weakness
    - c) Segmental sensory loss
    - d) EMG or NCV evidence of nerve root impingement
    - e) Cauda equina syndrome
    - f) Neurogenic bowel or bladder
    - g) Long tract abnormalitiesForaminal or central spinal stenosis causing only radiating pain (e.g. radiculopathic pain) is included only on Line 527.
- B) Spinal fusion procedures are included on Line 346 for patients with MRI evidence of moderate or severe central spinal stenosis only when one of the following conditions are met:
  - 1) spinal stenosis in the cervical spine (with or without spondylolisthesis) which results in objective neurologic impairment as defined above OR
  - 2) spinal stenosis in the thoracic or lumbar spine caused by spondylolisthesis resulting in signs and symptoms of neurogenic claudication and which correlate with xray flexion/extension films showing at least a 5 mm translation OR
  - 3) pre-existing or expected post-surgical spinal instability (e.g. degenerative scoliosis >10 deg, >50% of facet joints per level expected to be resected)

For all other indications, spine surgery is included on Line 527.

The following interventions are not included on these lines due to lack of evidence of effectiveness for the treatment of conditions on these lines, including cervical, thoracic, lumbar, and sacral conditions:

- prolotherapy
- local injections
- botulinum toxin injection



**GUIDELINE NOTE 37, SURGICAL INTERVENTIONS FOR CONDITIONS OF THE BACK AND SPINE OTHER THAN SCOLIOSIS (CONT'D)**

- intradiscal electrothermal therapy
- therapeutic medial branch block
- coblation nucleoplasty
- percutaneous intradiscal radiofrequency thermocoagulation
- radiofrequency denervation
- corticosteroid injections for cervical pain

Corticosteroid injections for low back pain with or without radiculopathy are only included on Line 527.

The development of this guideline note was informed by HERC coverage guidances on [Percutaneous Interventions for Low Back Pain](#), [Percutaneous Interventions for Cervical Spine Pain](#) and [Low Back Pain: Corticosteroid Injections](#). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 38, SUBTALAR ARTHROEREISIS**

*Line 377*

Procedure code S2117 is only covered when not incorporating an implant device.

**GUIDELINE NOTE 39, ENDOMETRIOSIS AND ADENOMYOSIS**

*Lines 1,395*

- A) Hysterectomy, with or without adnexectomy, for endometriosis may be appropriate when all of the following are documented (1-4):
- 1) Patient history of (a and b):
    - a) Prior detailed operative description or histologic diagnosis of endometriosis
    - b) Presence of pain for more than 6 months with negative effect on patient's quality of life
  - 2) Failure of a 3-month therapeutic trial with both of the following (a and b), unless there are contraindications to use:
    - a) Hormonal therapy (i or ii):
      - i) Oral contraceptive pills or patches, progesterone-containing IUDs, injectable hormone therapy, or similar
      - ii) Agents for inducing amenorrhea (e.g., GnRH analogs or danazol)
    - b) Nonsteroidal anti-inflammatory drugs
  - 3) Nonmalignant cervical cytology, if cervix is present
  - 4) Negative preoperative pregnancy test result unless patient is postmenopausal or has been previously sterilized
- B) Hysterectomy, with or without adnexectomy, for adenomyosis may be appropriate when all of the following are documented (1-5):
- 1) Patient history of dysmenorrhea, pelvic pain or abnormal uterine bleeding for more than six months with a negative effect on her quality of life.
  - 2) Failure of a six-month therapeutic trial with both of the following (a and b), unless there are contraindications to use:
    - a) Hormonal therapy (i or ii):
      - i) Oral contraceptive pills or patches, progesterone-containing IUDs, injectable hormone therapy, or similar
      - ii) Agents for inducing amenorrhea (e.g., GnRH analogs or danazol)
    - b) Nonsteroidal anti-inflammatory drugs
  - 3) One of the following (a or b):
    - a) Endovaginal ultrasound suspicious for adenomyosis (presence of abnormal hypoechoic myometrial echogenicity or presence of small myometrial cysts)
    - b) MRI showing thickening of the junctional zone > 12mm
  - 4) Nonmalignant cervical cytology, if cervix is present
  - 5) Negative preoperative pregnancy test unless patient is postmenopausal or has been previously sterilized

**GUIDELINE NOTE 40, UTERINE LEIOMYOMA**

*Line 403*

Hysterectomy, myomectomy, or uterine artery embolization for leiomyomata may be indicated when all of the following are documented (A-D):

- A) One of the following (1 or 2):
- 1) Patient history of 2 out of 3 of the following (a, b and c):
    - a. Leiomyomata enlarging the uterus to a size of 12 weeks or greater gestation
    - b. Pelvic discomfort caused by myomata (i or ii or iii):
      - i) Chronic lower abdominal, pelvic or low back pressure
      - ii) Bladder dysfunction not due to urinary tract disorder or disease
      - iii) Rectal pressure and bowel dysfunction not related to bowel disorder or disease
    - c. Rapid enlargement causing concern for sarcomatous changes of malignancy
  - 2) Leiomyomata as probable cause of excessive uterine bleeding evidenced by (a, b, c and d):
    - a. Profuse bleeding lasting more than 7 days or repetitive periods at less than 21-day intervals
    - b. Anemia due to acute or chronic blood loss (hemoglobin less than 10 or hemoglobin less than 11 g/dL if use of iron is documented)



**GUIDELINE NOTE 40, UTERINE LEIOMYOMA (CONT'D)**

- c. Documentation of mass by sonography
- d. Bleeding causes major impairment or interferes with quality of life
- B) Nonmalignant cervical cytology, if cervix is present
- C) Assessment for absence of endometrial malignancy in the presence of abnormal bleeding
- D) Negative preoperative pregnancy test result unless patient is postmenopausal or has been previously sterilized

**GUIDELINE NOTE 41, SCOLIOSIS**

*Line 361*

Non-surgical treatments of scoliosis (ICD-10-CM M41) are included on Line 361 when

- 1) the scoliosis is considered clinically significant, defined as curvature greater than or equal to 25 degrees, or
- 2) there is curvature with a documented rapid progression.

Surgical treatments of scoliosis are included on Line 361

- 1) only for children and adolescents (age 20 and younger) with
- 2) a spinal curvature of greater than 45 degrees

**GUIDELINE NOTE 42, CHEMODENERVATION FOR CHRONIC MIGRAINE**

*Line 409*

Chemodenervation for treatment of chronic migraine (CPT 64615) is included on this line for prophylactic treatment of adults who meet all of the following criteria:

- A) have chronic migraine defined as headaches on at least 15 days per month of which at least 8 days are with migraine
- B) has not responded to or have contraindications to at least three prior pharmacological prophylaxis therapies (beta-blocker, calcium channel blocker, anticonvulsant or tricyclic antidepressant)
- C) treatment is administered in consultation with a neurologist or headache specialist.

Treatment is limited to two injections given 3 months apart. Additional treatment requires documented positive response to therapy. Positive response to therapy is defined as a reduction of at least 7 headache days per month compared to baseline headache frequency.

**GUIDELINE NOTE 43, LYMPHEDEMA**

*Line 421*

Lymphedema treatments are included on this line when medically appropriate. These services are to be provided by a licensed practitioner who is certified by one of the accepted lymphedema training certifying organizations or a graduate of one of the National Lymphedema Network accepted training courses within the past two years. The only accepted certifying organization at this time is LANA (Lymphology Association of North America; <http://www.clt-lana.org>). Treatments for lymphedema are not subject to the visit number restrictions found in Guideline Note 6 REHABILITATIVE AND HABILITATIVE THERAPIES.

It is the intent of the HERC that compression dressings/garments and other medical equipment needed for the treatment of lymphedema be covered even in the absence of ulcers or other complications.

**GUIDELINE NOTE 44, MENSTRUAL BLEEDING DISORDERS**

*Line 420*

Endometrial ablation or hysterectomy for abnormal uterine bleeding in Premenopausal women may be indicated when all of the following are documented (A-C):

- A) Patient history of (1, 2, 3, 4, and 5):
  - 1) Excessive uterine bleeding evidence by (a, b and c):
    - a) Profuse bleeding lasting more than 7 days or repetitive periods at less than 21-day intervals
    - b) Anemia due to acute or chronic blood loss (hemoglobin less than 10 g/dL or hemoglobin less than 11 g/dL if use of iron is documented)
    - c) Bleeding causes major impairment or interferes with quality of life
  - 2) Failure of hormonal treatment for a six-month trial period or contraindication to hormone use (oral contraceptive pills or patches, progesterone-containing IUDs, injectable hormone therapy, or similar)
  - 3) No current medication use that may cause bleeding, or contraindication to stopping those medications
  - 4) Endometrial sampling performed
  - 5) No evidence of treatable intrauterine conditions or lesions by (a, b or c):
    - a) Sonohysterography
    - b) Hysteroscopy
    - c) Hysterosalpingography
- B) Negative preoperative pregnancy test result unless patient has been previously sterilized
- C) Nonmalignant cervical cytology, if cervix is present



**GUIDELINE NOTE 45, CHEMODENERVATION OF THE BLADDER**

*Line 327*

Chemodenervation of the bladder (CPT 52287) is included on this line only for treatment of idiopathic detrusor over-activity or neurogenic detrusor over-activity (ICD-10-CM N32.81) in patients who have not responded to or been unable to tolerate at least two urinary incontinence antimuscarinic therapies (e.g. fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, trospium). Treatment is limited to 90 days, with additional treatment only if the patient shows documented positive response. Positive response to therapy is defined as a reduction of urinary frequency of 8 episodes per day or urinary incontinence of 2 episodes per day compared to baseline frequency.

**GUIDELINE NOTE 46, AGE-RELATED MACULAR DEGENERATION**

*Line 447*

Pegaptanib is only covered for minimally classic and occult lesions of wet macular degeneration.

**GUIDELINE NOTE 47, URINARY INCONTINENCE**

*Line 453*

Surgery for genuine stress urinary incontinence may be indicated when all of the following are documented (A-G):

- A) Patient history of (1, 2, and 3):
  - 1) Involuntary loss of urine with exertion
  - 2) Identification and treatment of transient causes of urinary incontinence, if present (e.g., delirium, infection, pharmaceutical causes, psychological causes, excessive urine production, restricted mobility, and stool impaction)
  - 3) Involuntary loss of urine on examination during stress (provocative test with direct visualization of urine loss) and low or absent post void residual
- B) Patient's voiding habits
- C) Physical or laboratory examination evidence of either (1 or 2):
  - 1) Urethral hypermobility
  - 2) Intrinsic sphincter deficiency
- D) Diagnostic workup to rule out urgency incontinence
- E) Negative preoperative pregnancy test result unless patient is postmenopausal or has been previously sterilized
- F) Nonmalignant cervical cytology, if cervix is present
- G) Patient required to have 3 months of alternative therapy (e.g., pessaries or physical therapy, including bladder training, pelvic floor exercises and/or biofeedback, as available). If limited coverage of physical therapy is available, patients should be taught pelvic floor exercises by their treating provider, physical therapist or trained staff, and have documented consistent practice of these techniques over the 3 month period.

**GUIDELINE NOTE 48, FRENULECTOMY/FRENULOTOMY**

*Line 344*

Frenulectomy/frenulotomy (D7960) is included on this line for the following situations:

- A) When deemed to cause gingival recession
- B) When deemed to cause movement of the gingival margin when frenum is placed under tension.
- C) Maxillary labial frenulectomy not covered until age 12 and above.

**GUIDELINE NOTE 49, WEARABLE CARDIAC DEFIBRILLATORS**

*Lines 69,99,111,189,281,347*

Wearable cardiac defibrillators (WCDs; CPT 93745, HCPCS K0606-K0609) are included on these lines for patients at high risk for sudden cardiac death who meet the medical necessity criteria for an implantable cardioverter defibrillator (ICD) as defined by the CMS 2005 National Coverage Determination but are unable to have an ICD implanted due to medical condition (e.g. ICD explanted due to infection with waiting period before ICD reinsertion or current medical condition contraindicates surgery). WCDs are not included on these lines for use during the waiting period for ICD implantation after myocardial infarction, coronary bypass surgery, or coronary artery stenting.

**GUIDELINE NOTE 50, PELVIC ORGAN PROLAPSE SURGERY**

*Line 464*

Hysterectomy, cystocele repair, and/or other surgery for pelvic organ prolapse may be indicated when all of the following are documented (A-E):

- A) Patient history of symptoms of pelvic prolapse such as:
  - 1) Complaints of the pelvic organs prolapsing at least to the introitus, and one or more of the following:
    - a) Low back discomfort or pelvic pressure, or
    - b) Difficulty in defecating, or
    - c) Difficulty in voiding
- B) For hysterectomy
  - 1) Nonmalignant cervical cytology, if cervix is present, and



**GUIDELINE NOTE 50, PELVIC ORGAN PROLAPSE SURGERY (CONT'D)**

- 2) Assessment for absence of endometrial malignancy in the presence of abnormal bleeding
- C) Physical examination is consistent with patient's symptoms of pelvic support defects indicating either symptomatic prolapse of the cervix, enterocele, cystocele, rectocele or prolapse of the vaginal vault
- D) Negative preoperative pregnancy test unless patient is postmenopausal or has been previously sterilized
- E) Patient required to have 3 months of alternative therapy (e.g., pessaries or physical therapy, including bladder training, pelvic floor exercises and/or biofeedback, as available). If limited coverage of physical therapy is available, patients should be taught pelvic floor exercises by their treating provider, physical therapist or trained staff, and have documented consistent practice of these techniques over the 3 month period.

**GUIDELINE NOTE 51, CHRONIC OTITIS MEDIA WITH EFFUSION**

*Lines 311,444,473*

Antibiotic and other medication therapy (including antihistamines, decongestants, and nasal steroids) are not indicated for children with chronic otitis media with effusion (OME) (without another appropriate diagnosis).

Patients with specific higher risk conditions (including craniofacial anomalies, Down's syndrome, and cleft palate, or documented speech and language delay) along with hearing loss and chronic otitis media with effusion are intended to be included on Line 311 or Line 444 for children up to and including age 7. Otherwise hearing loss associated with chronic otitis media with effusion (without those specific higher risk conditions) is only included on Line 473.

For coverage to be considered on Line 311, Line 444 or Line 473, there should be a 3 to 6 month watchful waiting period after diagnosis of otitis media with effusion, and if documented hearing loss is greater than or equal to 25dB in the better hearing ear, tympanostomy surgery may be indicated, given short- but not long- term improvement in hearing. Formal audiometry is indicated for children with chronic OME present for 3 months or longer. Children with language delay, learning problems, or significant hearing loss should have hearing testing upon diagnosis. Children with chronic OME who are not at risk for language delay (such as those with hearing loss <25dB in the better hearing ear) or developmental delay should be reexamined at 3- to 6-month intervals until the effusion is no longer present, significant hearing loss is identified, or structural abnormalities of the eardrum or middle ear are suspected.

Adenoidectomy is not indicated at the time of first pressure equalization tube insertion. It may be indicated in children aged 4 and older who are having their second set of tubes.

Removal of retained tympanostomy tubes requiring anesthesia (CPT code 69424) or as an office visit, is included on Line 422 as a complication, pairing with ICD-10-CM H74.8.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 52, CHRONIC ANAL FISSURE**

*Line 524*

Surgery for chronic anal fissure (ICD-10-CM K60.1) is included in this line with one or more of the following:

- A) Condition unresponsive to six to eight weeks of continuous treatment;
- B) Condition progresses in spite of six to eight weeks of treatment;
- C) Presence of pectenosis; and/or,
- D) Fissures that have previously healed but have recurred three or more times.

**GUIDELINE NOTE 53, BASIC PERIODONTICS**

*Line 219*

Only for the treatment of severe drug-induced hyperplasia (D4210, D4211, D4212). Payable only when there are pockets of 5 mm or greater (D4341).

**GUIDELINE NOTE 54, CONDUCT DISORDER**

*Line 477*

Conduct disorder rarely occurs in isolation from other psychiatric diagnosis, the patient should have documented screening for attention deficit/hyperactivity disorder (ADHD); chemical dependency (CD); mood disorders such as anxiety and/or depression; and physical, sexual, and family abuse or other trauma (PTSD).

**GUIDELINE NOTE 55, PELVIC PAIN SYNDROME**

*Line 529*

- A) Diagnostic MRI may be indicated for evaluation of pelvic pain to assess for Adenomyosis and to assist in the management of these challenging patients when all of the following are documented:
  - 1) Patient history of dysmenorrhea, pelvic pain or abnormal uterine bleeding for more than six months with a negative effect on her quality of life.
  - 2) Failure of a six-month therapeutic trial with both of the following (a and b), unless there are contraindications to use:



**GUIDELINE NOTE 55, PELVIC PAIN SYNDROME (CONT'D)**

- a) Hormonal therapy (i or ii):
    - i) Oral contraceptive pills or patches, progesterone-containing IUDs, injectable hormone therapy, or similar
    - ii) Agents for inducing amenorrhea (e.g., GnRH analogs or danazol)
  - b) Nonsteroidal anti-inflammatory drugs
  - 3) An endovaginal ultrasound within the past 12 months that shows no other suspected gynecological pathology if diagnostic MRI shows > 12mm thickening of the junctional zone, the presumptive diagnosis of adenomyosis is fulfilled. See Guideline Note 39.
- B) Hysterectomy for chronic pelvic pain in the absence of significant pathology may be Indicated when all of the following are documented (1-7):
- 1) Patient history of:
    - a) No treatable conditions or lesions found on laparoscopic examination
    - b) Pain for more than 6 months with negative effect on patient's quality of life
  - 2) Failure of a six-month therapeutic trial with both of the following (a and b), unless there are contraindications to use:
    - a) Hormonal therapy (i or ii):
      - i) Oral contraceptive pills or patches, progesterone-containing IUDs, injectable hormone therapy, or similar
      - ii) Agents for inducing amenorrhea (e.g., GnRH analogs or danazol)
    - b) Nonsteroidal anti-inflammatory drugs
  - 3) Evaluation of the following systems as possible sources of pelvic pain:
    - a) Urinary
    - b) Gastrointestinal
    - c) Musculoskeletal
  - 4) Evaluation of the patient's psychologic and psychosexual status for nonsomatic cause of symptoms
  - 5) Nonmalignant cervical cytology, if cervix is present
  - 6) Assessment for absence of endometrial malignancy in the presence of abnormal bleeding
  - 7) Negative preoperative pregnancy test unless patient is postmenopausal or as been previously sterilized

**GUIDELINE NOTE 56, NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE**

*Lines 361,401*

Patients seeking care for back pain should be assessed for potentially serious conditions ("red flag" symptoms requiring immediate diagnostic testing), as defined in Diagnostic Guideline D4. Patients lacking red flag symptoms should be assessed using a validated assessment tool (e.g. STarT Back Assessment Tool) in order to determine their risk level for poor functional prognosis based on psychosocial indicators.

For patients who are determined to be low risk on the assessment tool, the following services are included on these lines:

- Office evaluation and education,
- Up to four total visits, consisting of the following treatments: OMT/CMT, acupuncture, and PT/OT. Massage, if available, may be provided as part of these four total visits.
- First line medications: NSAIDs, acetaminophen, and/or muscle relaxers. Opioids may be considered as a second line treatment, subject to the limitations on coverage of opioids in Guideline Note 60 OPIOIDS FOR CONDITIONS OF THE BACK AND SPINE. See evidence table.

For patients who are determined to be medium- or high risk on the validated assessment tool, as well as patients undergoing opioid tapers as in Guideline Note 60 OPIOIDS FOR CONDITIONS OF THE BACK AND SPINE, the following treatments are included on these lines:

- Office evaluation, consultation and education
- Cognitive behavioral therapy. The necessity for cognitive behavioral therapy should be re-evaluated every 90 days and coverage will only be continued if there is documented evidence of decreasing depression or anxiety symptomatology, improved ability to work/function, increased self-efficacy, or other clinically significant, objective improvement.
- Prescription and over-the-counter medications; opioid medications subject to the limitations on coverage of opioids in Guideline Note 60 OPIOIDS FOR CONDITIONS OF THE BACK AND SPINE. See evidence table.
- The following evidence-based therapies, when available, may be provided: yoga, massage, supervised exercise therapy, intensive interdisciplinary rehabilitation. HCPCS S9451 is only included on Line 401 for the provision of yoga or supervised exercise therapy.
- A total of 30 visits per year of any combination of the following evidence-based therapies when available and medically appropriate. These therapies are only included on these lines if provided by a provider licensed to provide the therapy and when there is documentation of measurable clinically significant progress toward the therapy plan of care goals and objectives using evidence based objective tools (e.g. Oswestry, Neck Disability Index, SF-MPQ, and MSPQ).
  - 1) Rehabilitative therapy (physical and/or occupational therapy), if provided according to Guideline Note 6 REHABILITATIVE AND HABILITATIVE THERAPIES. Rehabilitation services provided under this guideline also count towards visit totals in Guideline Note 6. CPT 97124 is included in this category.
  - 2) Chiropractic or osteopathic manipulation
  - 3) Acupuncture

Mechanical traction (CPT 97012) is not included on these lines, due to evidence of lack of effectiveness for treatment of back and neck conditions.

The development of this guideline note was informed by HERC coverage guidances on [Low Back Pain Non-Pharmacologic, Non-Invasive Intervention, Low Back Pain, Pharmacological and Herbal Therapies](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.



**GUIDELINE NOTE 56, NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE (CONT'D)****Evidence Table of Effective Treatments for the Management of Low Back Pain**

Intervention Category*	Intervention	Acute < 4 Weeks	Subacute & Chronic > 4 Weeks
Self-care	Advice to remain active	●	●
	Books, handout	●	●
	Application of superficial heat	●	
Nonpharmacologic therapy	Spinal manipulation	●	●
	Exercise therapy		●
	Massage		●
	Acupuncture		●
	Yoga		●
	Cognitive-behavioral therapy		●
	Progressive relaxation		●
Pharmacologic therapy (Carefully consider risks/harms)	Acetaminophen	●	●
	NSAIDs	●(▲)	●(▲)
	Skeletal muscle relaxants	●	
	Antidepressants (TCA)		●
	Benzodiazepines**	●(▲)	●(▲)
	Tramadol, opioids**	●(▲)	●(▲)
Interdisciplinary therapy	Intensive interdisciplinary rehabilitation		●
<p>● Interventions supported by grade B evidence (at least fair-quality evidence of moderate benefit, or small benefit but no significant harms, costs, or burdens). No intervention was supported by grade "A" evidence (good-quality evidence of substantial benefit).</p> <p>▲ Carries greater risk of harms than other agents in table.</p>			

NSAIDs = nonsteroidal anti-inflammatory drugs; TCA = tricyclic antidepressants.

\*These are general categories only. Individual care plans need to be developed on a case by case basis. For more detailed information please see: <http://www.annals.org/content/147/7/478.full.pdf>

\*\*Associated with significant risks related to potential for abuse, addiction and tolerance. This evidence evaluates effectiveness of these agents with relatively short term use studies. Chronic use of these agents may result in significant harms.

**GUIDELINE NOTE 57, PELVIC PHYSICAL THERAPY FOR INTERSTITIAL CYSTITIS**

Line 327

Pelvic physical therapy (CPT 97140 and 97161-97164) is included on this line only for treatment of interstitial cystitis in patients who present with pelvic floor tenderness. Such pelvic PT is only included on this line when provided by professionals trained and experienced in pelvic floor therapy and as limited in Guideline Note 6 REHABILITATIVE AND HABILITATIVE THERAPIES.

**GUIDELINE NOTE 58, IMPULSE DISORDERS**

Line 544

Impulse disorders rarely occur in isolation from other psychiatric diagnosis, thus the Patient should have documented screening for attention deficit/hyperactivity disorder (ADHD); chemical dependency (CD); mood disorders such as anxiety and/or depression; and physical, sexual, and family abuse or other trauma (PTSD).

**GUIDELINE NOTE 59, DYSMENORRHEA**

Line 555

Hysterectomy for dysmenorrhea may be indicated when all of the following are documented (A-G):

- A) Patient history of:
- 1) No treatable conditions or lesions found on laparoscopic examination
  - 2) Pain for more than 6 months with negative effect on patient's quality of life



**GUIDELINE NOTE 59, DYSMENORRHEA (CONT'D)**

- B) Failure of a six-month therapeutic trial with both of the following (1 and 2), unless there are contraindications to use:
  - 1) Hormonal therapy (a or b):
    - a) Oral contraceptive pills or patches, progesterone-containing IUDs, injectable hormone therapy, or similar
    - b) Agents for inducing amenorrhea (e.g., GnRH analogs or danazol)
  - 2) Nonsteroidal anti-inflammatory drugs
- C) Evaluation of the following systems as possible sources of pelvic pain:
  - 1) Urinary
  - 2) Gastrointestinal
  - 3) Musculoskeletal
- D) Evaluation of the patient's psychologic and psychosexual status for nonsomatic cause of symptoms
- E) Nonmalignant cervical cytology, if cervix is present
- F) Assessment for absence of endometrial malignancy in the presence of abnormal bleeding
- G) Negative preoperative pregnancy test unless patient is postmenopausal or has been previously sterilized

**GUIDELINE NOTE 60, OPIOIDS FOR CONDITIONS OF THE BACK AND SPINE**

*Lines 346,361,401,527*

Opioid medications are only included on these lines under the following criteria:

For acute injury, acute flare of chronic pain, or after surgery:

- 1) During the first 6 weeks opioid treatment is included on these lines ONLY:
  - a) When each prescription is limited to 7 days of treatment, AND
  - b) For short acting opioids only, AND
  - c) When one or more alternative first line pharmacologic therapies such as NSAIDs, acetaminophen, and muscle relaxers have been tried and found not effective or are contraindicated, AND
  - d) When prescribed with a plan to keep active (home or prescribed exercise regime) and with consideration of additional therapies such as spinal manipulation, physical therapy, yoga, or acupuncture, AND
  - e) There is documented verification that the patient is not high risk for opioid misuse or abuse.
- 2) Treatment with opioids after 6 weeks, up to 90 days after the initial injury/flare/surgery is included on these lines ONLY:
  - a) With documented evidence of improvement of function of at least thirty percent as compared to baseline based on a validated tools (e.g. Oswestry, Neck Disability Index, SF-MPQ, and MSPQ).
  - b) When prescribed in conjunction with therapies such as spinal manipulation, physical therapy, yoga, or acupuncture.
  - c) With verification that the patient is not high risk for opioid misuse or abuse. Such verification may involve
    - i) Documented verification from the state's prescription monitoring program database that the controlled substance history is consistent with the prescribing record
    - ii) Use of a validated screening instrument to verify the absence of a current substance use disorder (excluding nicotine) or a history of prior opioid misuse or abuse
    - iii) Administration of a baseline urine drug test to verify the absence of illicit drugs and non-prescribed opioids.
  - d) Each prescription must be limited to 7 days of treatment and for short acting opioids only
- 3) Chronic opioid treatment (>90 days) after the initial injury/flare/surgery is not included on these lines except for the taper process described below.

Transitional coverage for patients on long-term opioid therapy as of July 1, 2016:

For patients on covered chronic opioid therapy as of July 1, 2016, opioid medication is included on these lines only from July 1, 2016 to December 31, 2016. During the period from January 1, 2017 to December 31, 2017, continued coverage of opioid medications requires an individual treatment plan developed by January 1, 2017 which includes a taper with an end to opioid therapy no later than January 1, 2018. Taper plans must include nonpharmacological treatment strategies for managing the patient's pain based on Guideline Note 56 NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE. If a patient has developed dependence and/or addiction related to their opioids, treatment is available on Line 4 SUBSTANCE USE DISORDER.

**GUIDELINE NOTE 61, HOSPITALIZATION FOR ACUTE VIRAL INFECTIONS**

*Lines 140,533,546,550,612*

Most acute viral infections are self-limited (e.g. colds, infectious mononucleosis, gastroenteritis). However, some viral infections such as aseptic meningitis, or severe gastroenteritis may require hospitalization to treat the complications of the primary disease.

Accepted coding practices insist that the underlying condition in these cases be the principle diagnosis. For example, complicated viral pneumonia requiring respiratory support with a ventilator would have a principle diagnosis of viral pneumonia and a secondary diagnosis of respiratory failure. Since the diagnosis code for viral pneumonia has historically appeared only on a non-funded line, treatment has not been reimbursable regardless of the severity of the disease. In contrast, the code for viral gastroenteritis appears on Line 146 and any necessary outpatient or inpatient services would be covered.

Reimbursement for the treatment of certain conditions appearing low on the Prioritized List should be provided in severe cases of the diseases identified on the following four lines.

Line: 550



**GUIDELINE NOTE 61, HOSPITALIZATION FOR ACUTE VIRAL INFECTIONS (CONT'D)**

Condition: OTHER NONINFECTIOUS GASTROENTERITIS AND COLITIS  
Treatment: MEDICAL THERAPY

Treatment of non-infectious gastroenteritis of significant severity that is associated with dehydration should be a covered service if the case fulfills the requirement of hospital admission guidelines using an index of severity of illness.

Line: 533  
Condition: VIRAL, SELF-LIMITING ENCEPHALITIS, MYELITIS AND ENCEPHALOMYELITIS  
Treatment: MEDICAL THERAPY

Treatment of viral encephalitis, myelitis and encephalomyelitis of significant severity that is associated with either obtundation or dehydration should be a covered service if the case fulfills the requirement of hospital admission guidelines using an index of severity of illness.

Line: 546  
Condition: ASEPTIC MENINGITIS  
Treatment: MEDICAL THERAPY

Treatment of aseptic meningitis of significant severity that is associated with either obtundation or dehydration should be a covered service if the case fulfills the requirement of hospital admission guidelines using an index of severity of illness.

Line: 611  
Condition: ACUTE UPPER RESPIRATORY INFECTIONS AND COMMON COLD  
Treatment: MEDICAL THERAPY

Line: 612  
Condition: OTHER VIRAL INFECTIONS  
Treatment: MEDICAL THERAPY

Line: 649  
Condition: INFECTIOUS DISEASES WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY  
Treatment: EVALUATION

Treatment of acute infectious disease that is associated with respiratory failure, obtundation/altered mental status, or dehydration should be a covered service if the case fulfills the requirement of hospital admission guidelines using an index of severity of illness.

**GUIDELINE NOTE 62, NEGATIVE PRESSURE WOUND THERAPY**

*Lines 8,27,47,80,206,208,236,285,379,422*

Negative pressure wound therapy (CPT 97605-97608) is included on these lines only for patients who:

- Have wounds that are refractory to or have failed standard therapies;
- Are not suitable candidates for surgical wound closure; or,
- Are at high risk for delayed or non-healing wounds due to factors such as compromised blood flow, diabetic complications, wounds with high risk of fecal contamination, extremely exudative wounds, and similar situations.

**GUIDELINE NOTE 63, HYDROCELE REPAIR**

*Line 168*

Excision of hydrocele is only covered for children age 18 and younger with hydroceles which persist after 18 months of age.

**GUIDELINE NOTE 64, PHARMACIST MEDICATION MANAGEMENT**

*Included on all lines with evaluation & management (E&M) codes*

Pharmacy medication management services must be provided by a pharmacist who has:

- 1) A current and unrestricted license to practice as a pharmacist in Oregon.
- 2) Documentation must be provided for each consultation and must reflect communication with the patient's primary care provider. Documentation should model SOAP charting; must include patient history, provider assessment and treatment plan; follow up instructions; be adequate so that the information provided supports the assessment and plan; and must be retained in the patient's medical record and be retrievable.

**GUIDELINE NOTE 65, TELEPHONE AND EMAIL CONSULTATIONS**

*Included on all lines with evaluation & management (E&M) codes*

Telephone and email consultations (CPT 98966-98969) must meet the following criteria:

- 1) Patient must have a pre-existing relationship with the provider as demonstrated by at least one prior office visit within the past 12 months.
- 2) E-visits must be provided by a physician or licensed provider within their scope of practice.



**GUIDELINE NOTE 65, TELEPHONE AND EMAIL CONSULTATIONS (CONT'D)**

- 3) Documentation should model SOAP charting; must include patient history, provider assessment, and treatment plan; follow up instructions; be adequate so that the information provided supports the assessment and plan; must be retained in the patient's medical record and be retrievable.
- 4) Telephone and email consultations must involve permanent storage (electronic or hard copy) of the encounter.
- 5) Telephone and email consultations must meet HIPAA standards for privacy.
- 6) There needs to be a patient-clinician agreement of informed consent for E-visits by email. This should be discussed with and signed by the patient and documented in the medical record.

Examples of reimbursable telephone and email consultations include but are not limited to:

- 1) Extended counseling when person-to-person contact would involve an unwise delay.
- 2) Treatment of relapses that require significant investment of provider time and judgment.
- 3) Counseling and education for patients with complex chronic conditions.

Examples of non-reimbursable telephone and email consultations include but are not limited to:

- 1) Prescription renewal.
- 2) Scheduling a test.
- 3) Scheduling an appointment.
- 4) Reporting normal test results.
- 5) Requesting a referral.
- 6) Follow up of medical procedure to confirm stable condition, without indication of complication or new condition.
- 7) Brief discussion to confirm stability of chronic problem and continuity of present management.

**GUIDELINE NOTE 66, CERVICAL DYSPLASIA**

*Line 25*

Work up and treatment of cervical dysplasia should follow the American Society for Cervical Colposcopy and Pathology guidelines as published in the Journal of Lower Genital Tract Disease, April 2013.

**GUIDELINE NOTE 67, ENZYME REPLACEMENT THERAPY**

*Lines 147,660*

Enzyme replacement therapy for infantile Pompe's disease is included on Line 147. All other enzyme replacement therapies for inborn errors of metabolism are included on Line 660.

**GUIDELINE NOTE 68, HYSTEROSCOPIC BILATERAL FALLOPIAN TUBE OCCLUSION**

*Line 6*

Placement of permanent implants in the fallopian tubes to induce bilateral occlusion (CPT code 58565) is covered only if the procedure is done in the office setting, not in the ambulatory surgical center or hospital setting.

Hysterosalpingography (58340, 74740) is covered only for the follow-up testing after placement of permanent implants in the fallopian tubes to induce bilateral occlusion.

**GUIDELINE NOTE 69, ELECTROCONVULSIVE THERAPY (ECT)**

*Lines 7,22,26*

Electroconvulsive therapy (ECT; CPT 90870) is included on these lines for the treatment of major depressive disorder, bipolar disorder, schizophrenic disorder, or schizoaffective disorder when one or more of the following conditions are present:

- 1) Acute suicidality with high risk of acting out suicidal thoughts
- 2) Psychotic features
- 3) Rapidly deteriorating physical status due to complications from the depression, such as poor oral intake
- 4) Catatonia
- 5) History of poor response to multiple adequate trials of medications and/or combination treatments, or the patient is unable or unwilling to comply with or tolerate side effects of available medications, or has a co-morbid medical condition that prevents the use of available medications
- 6) History of good response to ECT during an earlier episode of the illness
- 7) The patient is pregnant and has severe mania or depression, and the risks of providing no treatment outweigh the risks of providing ECT

The frequency and number of treatments need to be determined by the severity of illness and by the relative benefits and risks of ECT treatment. During the course of ECT, it is important to monitor therapeutic responses and adverse effects of treatment. Continuation treatment of patients who have responded to ECT consists of treatment with antidepressant medications and/or a tapering schedule of ECT treatments. Continuation treatment reduces the risk of relapse and should be offered to all patients who respond to ECT. Continuation ECT treatments should be tapered and discontinued as the patient's clinical condition allows. Maintenance treatment with ECT is indicated to prevent recurrence of depression in patients whose remission of symptoms cannot be maintained with pharmacologic antidepressant treatment.



**GUIDELINE NOTE 70, HEART-KIDNEY TRANSPLANTS**

*Line 264*

Patients under consideration for heart/kidney transplant must qualify for each individual type of transplant under current DMAP administrative rules and transplant center criteria with the exception of any exclusions due to heart and/or kidney disease. Qualifying renal disease is limited to Stage V or VI.

**GUIDELINE NOTE 71, HIP RESURFACING**

*Line 356*

Hip resurfacing is a covered service for patients who are likely to outlive a traditional prosthesis and who would otherwise require a total hip replacement, and should only be done by surgeons with specific training in this technique.

The following criteria are required to be met for coverage of this procedure:

- A) The diagnosis of osteoarthritis or inflammatory arthritis
- B) Failure of nonsurgical management
- C) The device must be FDA approved

Patients who are candidates for hip resurfacing must not be:

- A) Patients with active or suspected infection in or around the hip joint, or sepsis
- B) Patients who are skeletally immature
- C) Patients with any vascular insufficiency, muscular atrophy, or neuromuscular disease severe enough to compromise implant stability or postoperative recovery
- D) Patients with bone stock inadequate to support the device, including severe osteopenia or a family history of severe osteoporosis or osteopenia
- E) Patients with osteonecrosis or avascular necrosis with >50% involvement of the femoral head
- F) Patients with multiple cysts of the femoral head
- G) Females of childbearing age
- H) Patients with known moderate-to-severe renal insufficiency
- I) Patients who are immunosuppressed with diseases such as AIDS or persons receiving high doses of corticosteroids
- J) Patients who are severely overweight
- K) Patients with known or suspected metal sensitivity

The development of this guideline note was informed by a HERC [coverage guidance](#). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 72, CONGENITAL UROLOGIC CONDITIONS**

*Lines 87,94,432,656*

The following conditions are included on these Lines 87, 94 and 432 only for children aged 18 and younger. For adults, these conditions are included on Line 656.

- ICD-10-CM Q54.0 (Hypospadias, balanic)
- ICD-10-CM Q55.22 (Retractile testicle)
- ICD-10-CM Q60.3 (Renal hypoplasia, unilateral)
- ICD-10-CM Q62.4 (Agenesis of ureter)
- ICD-10-CM Q62.5 (Duplication of ureter)
- ICD-10-CM Q62.60 (Accessory kidney)
- ICD-10-CM Q62.61 (Deviation of ureter)
- ICD-10-CM Q62.62 (Displacement of ureter)
- ICD-10-CM Q63 (Other congenital malformations of kidney)

**GUIDELINE NOTE 73, PENILE ANOMALIES**

*Lines 432,656*

Anomalies of the penis (ICD-10-CM Q54.4, Q55.5 and Q55.6) are included on Line 432 only when they

- A. Are associated with hypospadias, OR
- B. Result in documented urinary retention, OR
- C. Result in repeated urinary tract infections, OR
- D. Result in recurrent infections such as meatitis or balanitis, OR
- E. Involve 35 degrees of curvature or greater for conditions resulting in lateral or ventral curvature, OR
- F. Involve 60 degrees of rotation or greater for conditions resulting in penile torsion, OR
- G. Involve aplasia/congenital absence of the penis.

Otherwise, these diagnoses are included on Line 656.



**GUIDELINE NOTE 74, GROWTH HORMONE TREATMENT**

*Lines 40,386,467*

Treatment with growth hormone is included only for children with: pituitary dwarfism, Turner's syndrome, Prader-Willi-syndrome, Noonan's syndrome, short stature homeobox-containing gene (SHOX), chronic kidney disease (stages 3, 4, 5 or 6) and those with renal transplant. Treatment with growth hormone should continue only until adult height as determined by bone age is achieved. Treatment is not included for isolated deficiency of human growth hormone or other conditions in adults.

**GUIDELINE NOTE 75, APPLIED BEHAVIOR ANALYSIS FOR AUTISM SPECTRUM DISORDER**

*Line 193*

Applied behavioral analysis (ABA), including early intensive behavioral intervention (EIBI), represented by CPT codes 0359T-0374T, is included on Line 193 AUTISM SPECTRUM DISORDERS for the treatment of autism spectrum disorders.

ABA services are provided in addition to any rehabilitative services (e.g. physical therapy, occupational therapy, speech therapy) included in Guideline Note 6 REHABILITATIVE AND HABILITATIVE THERAPIES that are indicated for other acute qualifying conditions.

Individuals ages 1-12

*Intensive interventions*

Specifically, EIBI (for example, UCLA/Lovaas or Early Start Denver Model), is included on this line.

For a child initiating EIBI therapy, EIBI is included for up to six months. Ongoing coverage is based on demonstrated progress towards meaningful predefined objectives (objectives should be achieved as a result of the EIBI, over and beyond gains that would be expected to arise from maturation alone) using a standardized, multimodal assessment, no more frequently than every six months. Examples of such assessments include Vineland, IQ tests (Mullen, WPPSI, WISC-R), language measures, behavior checklists (CBCL, ABC), and autistic symptoms measures (SRS).

The evidence does not lead to a direct determination of optimal intensity. Studies of EIBI ranged from 15-40 hours per week. Through Oregon's Senate Bill 365, other payers are mandated to cover a minimum of 25 hours per week of ABA. There is no evidence that increasing intensity of therapy yields improves outcomes. Studies for these interventions had a duration from less than one year up to 3 years.

*Less intensive ABA-based interventions*

If EIBI is not indicated, has been completed, or there is not sufficient progress toward multidimensional goals, then less intensive ABA-based interventions (such as parent training, play/interaction based interventions, and joint attention interventions) are included on this line to address core symptoms of autism and/or specific problem areas. Initial coverage is provided for six months. Ongoing coverage is based on demonstrated progress towards meaningful predefined objectives, with demonstration of medical appropriateness and/or emergence of new problem behaviors.

Effective interventions from the research literature had lower intensity than EIBI, usually a few hours per week to a maximum of 16 hours per week, divided into daily, twice-daily or weekly sessions, over a period of several months.

*Parent/caregiver involvement*

Parent/caregiver involvement and training is recommended as a component of treatment.

Individuals ages 13 and older

Intensive ABA is not included on this line.

Targeted ABA-based behavioral interventions to address problem behaviors, are included on this line. The quality of evidence is insufficient to support these interventions in this population. However, due to strong caregiver values and preferences and the potential for avoiding suffering and expense in dealing with unmanageable behaviors, targeted interventions may be reasonable. Behaviors eligible for coverage include those which place the member at risk for harm or create significant daily issues related to care, education, or other important functions. Ongoing coverage is based on demonstrated progress towards meaningful predefined objectives, with demonstration of medical appropriateness and/or emergence of new problem behaviors.

Very low quality evidence is available to illustrate needed intensity and duration of intervention. In the single-subject research design literature, frequency and duration of interventions were highly variable, with session duration ranging from 30 seconds to 3 hours, number of sessions ranging from a total of three to 8 times a day, and duration ranging from 1 to 20 weeks. These interventions were often conducted in inpatient or residential settings and studies often included patients with intellectual disabilities, some of which were not diagnosed with autism.

Parent/caregiver involvement and training is encouraged.



**GUIDELINE NOTE 76, DIAGNOSTIC TESTING FOR LIVER FIBROSIS TO GUIDE TREATMENT OF HEPATITIS C IN NON-CIRRHOTIC PATIENTS**

*Line 199*

Given that a fibrosis score of  $\geq F2$  is the threshold for antiviral treatment of Hepatitis C, the following are included on this line:

Imaging tests:

- Transient elastography (FibroScan®)
- Acoustic radiation force impulse imaging (ARFI) (Virtual Touch™ tissue quantification, ElastPQ)
- Shear wave elastography (SWE) (Aixplorer®)

Blood tests (only if imaging tests are unavailable):

- Enhanced Liver Fibrosis (ELF™)
- Fibrometer™
- FIBROSpect® II
- FibroSure® (FibroTest®)

If a fibrosis score of  $\geq F3$  is the threshold for antiviral treatment of Hepatitis C, one or more of the following are included on this line:

Imaging tests:

- Transient elastography (FibroScan®)
- Acoustic radiation force impulse imaging (ARFI)
- Shear wave elastography (SWE)

Magnetic resonance elastography is included on this line for  $\geq F2$  or  $\geq F3$  only when at least one imaging test (FibroScan, ARFI, and SWE) has resulted in indeterminate results, a second one is similarly indeterminate, contraindicated or unavailable, and MRE is readily available.

The following tests are not included on this line (or any other line):

- Real time tissue elastography
- Hepascore (FibroScore)

Noninvasive tests are covered no more often than once per year.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 77, TIPS PROCEDURE**

*Lines 56,217,280,334*

TIPS procedure (CPT code 37182, 37183) is included on these lines for patients who:

- A) Have failed sclerotherapy and have acute bleeding from varices; or
- B) Have failed sclerotherapy and have had 2 or more episodes of re-bleeding requiring a transfusion during a 2-week period; or
- C) Requires bleeding control from varices and surgery is contraindicated; or
- D) Are liver transplant candidates who require bleeding control from varices; or
- E) Have severe debilitating ascites or hepatic hydrothorax refractory to medical management (e.g., oral diuretics and repeated large-volume paracentesis).

**GUIDELINE NOTE 78, HEPATIC METASTASES**

*Line 315*

ICD-10-CM C78.7 Hepatic metastases are included on this line only when:

- A) Treatment of the primary tumor is covered on a funded line in accordance with the criteria in Guideline Note 12 TREATMENT OF CANCER WITH LITTLE OR NO BENEFIT;
- B) There are no other extrahepatic metastases; and,
- C) The only treatment covered is hepatectomy/resection of liver (CPT codes 47120, 47122, 47125 or 47130).

**GUIDELINE NOTE 79, BREAST RECONSTRUCTION**

*Line 191*

Breast reconstruction is only covered after mastectomy as a treatment for breast cancer or as prophylactic treatment for the prevention of breast cancer in a woman who qualifies under Guideline Note 3, and must be completed within 5 years of initial mastectomy.

Breast reconstruction may include contralateral reduction mammoplasty (CPT 19318) or contralateral mastopexy (CPT 19316). Mastopexy is only to be covered when contralateral reduction mammoplasty is inappropriate for breast reconstruction and mastopexy will accomplish the desired reconstruction result.



**GUIDELINE NOTE 80, REPAIR OF NOSE TIP**

*Line 300*

Nose tip repair (CPT 30460) is included on this line only to be used in conjunction with codes 40700, 40701, 40702 or 40720. If not done in the context of a larger cleft palate/lip surgery, then nose tip repair is only included on this line if required for correction of physical functioning.

**GUIDELINE NOTE 81, BUERGER'S DISEASE**

*Lines 236,651*

Buerger's disease (ICD-10-CM I73.1) is included on Line 236 only when ulceration or gangrene is present. Otherwise, this diagnosis is included on Line 651. ICD-10-CM I73.1 does not pair on Line 236 with revascularization procedures, bypass graft procedures, or angioplasty.

**GUIDELINE NOTE 82, EARLY INTERVENTION FOR PSYCHOSIS**

*Lines 22,26,277*

- A) These lines include "early intervention for psychosis," a multidisciplinary specialty team-based intervention that includes:
- B) Psychiatric medication management
- C) Individual counseling
- D) Family group therapy
- E) Family individual therapy

The goal of the early intervention is to minimize harms of a first outbreak of psychosis and improve long-term functioning.

**GUIDELINE NOTE 83, HIP CORE DECOMPRESSION**

*Line 356*

Hip Core Decompression (S2325) is covered only for early/pre-collapse (stage I or II; before X-ray changes are evident) avascular necrosis of the hip (femoral head and/or neck).

**GUIDELINE NOTE 84, MEDICAL NUTRITION THERAPY FOR EPILEPSY**

*Line 30*

Medical Nutrition Therapy (CPT 97802-97804) is included on this line only for training in the ketogenic diet for children with epilepsy in cases where the child has failed or not tolerated conventional therapy.

**GUIDELINE NOTE 85, ELECTIVE INDUCTION OF LABOR**

*Line 1*

Induction of labor is covered for:

- Gestational age beyond 41 weeks 0 days
- Prelabor rupture of membranes, term
- Fetal demise
- Preeclampsia, term (severe or mild)
- Eclampsia
- Chorioamnionitis
- Diabetes, pre-existing and gestational
- Placental abruption
- Preeclampsia, preterm (severe or mild)
- Severe preeclampsia, preterm
- Cholestasis of pregnancy
- Preterm, prelabor rupture of membranes;
- Gastroschisis
- Twin gestation
- Maternal medical conditions (e.g., renal disease, chronic pulmonary disease, chronic hypertension, cardiac disease, antiphospholipid syndrome)
- Gestational hypertension
- Fetal compromise (e.g. isoimmunization, oligohydramnios)
- Intrauterine growth restriction/Small for gestational age, term
- Elective purposes, >39 weeks 0 days to <41 weeks 0 days (without a medical or obstetrical indication) with a favorable cervix (for example, with a Bishop score ≥6)

Induction of labor is not covered for the following:

- Macrosomia (in the absence of maternal diabetes)



**GUIDELINE NOTE 85, ELECTIVE INDUCTION OF LABOR (CONT'D)**

- Elective purposes, >39 weeks 0 days to <41 weeks 0 days (without a medical or obstetrical indication) with an unfavorable cervix (for example, a Bishop score <6)
- Elective purposes <39 weeks (without a medical or obstetrical indication)
- Intrauterine growth restriction/Small for gestational age, preterm (without other evidence of fetal compromise)

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 86, ORGANIC MENTAL DISORDERS**

*Line 202*

There is limited evidence of the effectiveness of mental health treatment of organic mental disorders. However, case management is can be critical. Effective treatments may be available for co-morbid conditions such as mood disorders. When treating co-morbid conditions associated with organic mental disorder, those conditions should be the primary diagnosis for billing purposes. The treatment of co-morbid mental health conditions should be consistent with the treatment methods, frequency, and duration normally applied to those diagnoses. Treatment of neurologic dysfunctions that may be seen in individuals with organic mental disorder are prioritized according to the four dysfunction lines found on the Prioritized List (Lines 71, 292, 345 and 377).

**GUIDELINE NOTE 87, INFLUENZA**

*Line 398*

Treatment and post-exposure prophylaxis of influenza should comply with state and national public health recommendations.

**GUIDELINE NOTE 88, USE OF PROGESTERONE CONTAINING IUDS FOR NON-CONTRACEPTIVE INDICATIONS**

*Lines 191,420,467*

Intrauterine device (IUD) insertion and removal (CPT 58300 and 58301) are included on these lines for use only with progesterone-containing IUDs. These CPT codes are covered only for

- A) menorrhagia (ICD-10-CM N92.0-N92.2 and N92.4)
- B) for uterine protection in women taking estrogen replacement therapy after premature ovarian failure (ICD-10-CM E28.310, E28.319, E28.39, E28.8, E28.9) or menopause (ICD-10-CM N95.1) ; and
- C) for uterine protection in women taking selective estrogen receptor modulators (SERMs).

**GUIDELINE NOTE 89, REVASCULARIZATION FOR CHRONIC STABLE ANGINA**

*Line 189*

Coronary revascularization with percutaneous coronary intervention (PCI; CPT 92920-92944) or coronary artery bypass surgery (CABG; CPT 33510-33516, 33517-33530, 33533-33536) is included on this line for patients with stable angina (ICD-10-CM I20, I25.111-119, I25.701-9, I25.711-9, I25.721-9, I25.731-9, I25.751-9, I25.761-9, I25.791-9, I25.89, I25.9) whose symptoms are not controlled with optimal medical therapy for angina or who cannot tolerate such therapy.

Optimal medical therapy for angina symptom control is defined as two or more antianginals (beta-blocker, nitrate, calcium channel blocker, or ranolazine) in addition to standard treatment for coronary artery disease.

For those with left main coronary artery stenosis or three-vessel coronary artery stenosis, CABG is included on this line with or without a trial of optimal medical therapy.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 90, COGNITIVE REHABILITATION**

*Lines 92,178,196,202,285,317,345,377*

Once physical stabilization from acute brain injury has occurred, as determined by an attending physician, cognitive rehabilitation (CPT 97532) is included on this line for a three month period. This three month period does not have to be initiated immediately following stabilization from the injury. For up to 3 years following the acute event, an additional 6 visits of cognitive rehabilitation are included on this line each time the patient has a major change in status resulting in a significantly improved prognosis. Cognitive rehabilitation is not included on this line for those in a vegetative state or for those who are unable or unwilling to participate in therapy.

**GUIDELINE NOTE 91, CARIES ARRESTING MEDICAMENT APPLICATION**

*Line 343*

D1354 is limited to silver diamine fluoride applications for the treatment (rather than prevention) of caries, with a maximum of two applications per year.



**GUIDELINE NOTE 92, ACUPUNCTURE**

*Lines 1,5,202,361,401,409,461,538*

Inclusion of acupuncture (CPT 97810-97814) on the Prioritized List has the following limitations:

**Line 1 PREGNANCY**

Acupuncture pairs on Line 1 for the following conditions and codes.

*Hyperemesis gravidarum*

ICD-10-CM: O21.0, O21.1

Acupuncture pairs with hyperemesis gravidarum when a diagnosis is made by the maternity care provider and referred for acupuncture treatment for up to 12 sessions of acupressure/acupuncture per pregnancy.

*Breech presentation*

ICD-10-CM: O32.1

Acupuncture (and moxibustion) is paired with breech presentation when a referral with a diagnosis of breech presentation is made by the maternity care provider, the patient is between 33 and 38 weeks gestation, for up to 6 session per pregnancy.

*Back and pelvic pain of pregnancy*

ICD-10-CM: O99.89

Acupuncture is paired with back and pelvic pain of pregnancy when referred by maternity care provider/primary care provider for up to 12 sessions per pregnancy.

**Line 5 TOBACCO DEPENDENCE**

Acupuncture is included on this line for a maximum of 12 sessions per quit attempt up to two quit attempts per year; additional sessions may be authorized if medically appropriate.

**Line 202 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS**

Acupuncture is paired with the treatment of post-stroke depression only. Treatments may be billed to a maximum of 30 minutes face-to-face time and limited to 12 total sessions per year, with documentation of meaningful improvement; patients may have additional visits authorized beyond these limits if medically appropriate.

**Line 361 SCOLIOSIS**

Acupuncture is included on this line with visit limitations as in Guideline Note 56 NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE.

**Line 401 CONDITIONS OF THE BACK AND SPINE**

Acupuncture is included on this line with visit limitations as in Guideline Note 56 NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE.

**Line 409 MIGRAINE HEADACHES**

Acupuncture pairs on Line 409 for migraine (ICD-10-CM G43.0, G43.1, G43.5, G43.7, G43.8, G43.9), for up to 12 sessions per year.

**Line 461 OSTEOARTHRITIS AND ALLIED DISORDERS**

Acupuncture pairs on Line 461 for osteoarthritis of the knee only (ICD-10-CM M17), for up to 12 sessions per year.

**\*Line 538 TENSION HEADACHES**

Acupuncture is included on Line 538 for treatment of tension headaches (ICD-10-CM G44.2), for up to 12 sessions per year.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

\*Below the current funding line.

**GUIDELINE NOTE 93, IMPLANTABLE GNRH ANALOG THERAPY**

*Line 187*

Use of drug delivery implant therapy for GnRH analogue therapy (such as histrelin) (CPT 11981-11983) is covered only when injectable depot medications (such as Lupron) are contraindicated or after such medications have been tried and complications preclude further use.

**GUIDELINE NOTE 94, PECTUS EXCAVATUM**

*Lines 400,525*

Pectus excavatum (ICD-10-CM Q67.6) is included on Line 400 only for patients with all of the following:

- 1) Severe deformity (Haller index >3.25) AND
- 2) Documented pulmonary or cardiac dysfunction demonstrated by either
  - a) Cardiac effects to include cardiac compression or displacement, bundle branch block or other cardiac pathology secondary to compression of the heart, OR
  - b) Pulmonary function studies demonstrating at least a moderately severe restrictive lung defect, AND
- 3) these conditions are reasonably expected to be relieved with surgery.

Otherwise, this condition is included on Line 525

ICD-10-CM Q79.8 is included on Line 400 only for Poland syndrome. Other diagnoses using this code are on Line 525. Surgical reconstruction of musculo-skeletal chest wall deformities associated with Poland's syndrome are only included on Line 400 when causing functional deficits.



**GUIDELINE NOTE 95, IMMUNE MODIFYING THERAPIES FOR MULTIPLE SCLEROSIS**

*Line 252*

Once a diagnosis of primary progressive or secondary progressive multiple sclerosis is reached, immune modifying therapies are no longer covered.

**GUIDELINE NOTE 96, TREATMENT OF BENIGN NEOPLASM OF URINARY ORGANS**

*Lines 215,509*

Treatment of benign urinary system tumors (ICD-10-CM D30.00-D30.02) are included on Line 215 with evidence of bleeding or urinary obstruction. Treatment of 1) oncocytoma which is >5 cm in size or symptomatic and 2) angiomyolipoma (AML) which is >5cm in women of child bearing age or in symptomatic men or women is covered. Otherwise, these diagnoses are included on Line 509.

**GUIDELINE NOTE 97, MANAGEMENT OF ACROMIOCLAVICULAR JOINT SPRAIN**

*Lines 417,605*

Sprain of acromioclavicular joint (ICD-10-CM S43.50-S43.52) is only included on Line 417 for Grade 4-6 sprains. Surgical management of these injuries is covered only after a trial of conservative therapy. Grade 1-3 acromioclavicular joint sprains are included only on Line 605.

**GUIDELINE NOTE 98, SIGNIFICANT INJURIES TO LIGAMENTS, TENDONS AND MENISCI**

*Lines 376,430,605*

Significant injuries to ligaments, tendons and/or menisci are those that result in clinically demonstrable joint instability or mechanical interference with motion. Significant injuries are covered on Line 376 or Line 430; non-significant injuries are included on Line 605.

**GUIDELINE NOTE 99, ROUTINE PRENATAL ULTRASOUND**

*Lines 1,35,37,63*

Routine ultrasound for the average risk pregnant woman is included on these lines for:

- A) One ultrasound in the first trimester for the purpose of identifying fetal aneuploidy or anomaly (between 11 and 13 weeks of gestation) and /or dating confirmation. In some instances, if a patient's LMP is truly unknown, a dating ultrasound may be indicated prior to an aneuploidy screen
- B) One ultrasound for the purpose of anatomy screening after 18 weeks gestation. For those using tobacco during pregnancy, additional counseling around smoking impacts on the fetus is included during this ultrasound.

Only one type of routine prenatal ultrasound should be covered in a single day (i.e., transvaginal or abdominal).

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 100, SMOKING AND SPINAL FUSION**

*Lines 47,150,201,255,346,361,400,476,527,556*

Non-emergent spinal arthrodesis (CPT 22532-22634) is limited to patients who are non-smoking and abstinent from all nicotine products for 6 months prior to the planned procedure, as shown by negative cotinine levels at least 6 months apart, with the second test within 1 month of the surgery date. Patients should be given access to appropriate smoking cessation therapy. Non-emergent spinal arthrodesis is defined as surgery for a patient with a lack of myelopathy or rapidly declining neurological exam.

**GUIDELINE NOTE 101, ARTIFICIAL DISC REPLACEMENT**

*Lines 346,527*

Artificial disc replacement (CPT 22856-22865) is included on these lines as an alternative to fusion only when all of the following criteria are met:

Lumbar artificial disc replacement

- A) Patients must first complete a structured, intensive, multi-disciplinary program for management of pain, if covered by the agency;
- B) Patients must be 60 years or under;
- C) Patients must meet FDA approved indications for use and not have any contraindications. FDA approval is device specific but includes:
  - Failure of at least six months of conservative treatment
  - Skeletally mature patient
  - Replacement of a single disc for degenerative disc disease at one level confirmed by patient history and imaging

Cervical artificial disc replacement

- D) Patients must meet FDA approved indications for use and not have any contraindications. FDA approval is device specific but includes:



**GUIDELINE NOTE 101, ARTIFICIAL DISC REPLACEMENT (CONT'D)**

- Skeletally mature patient
- Reconstruction of a single disc following single level discectomy for intractable symptomatic cervical disc disease (radiculopathy or myelopathy) confirmed by patient findings and imaging.

The development of this guideline note was informed by a HERC [coverage guidance](#). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 102, REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION**

*Line 7*

Repetitive transcranial magnetic stimulation (CPT 90867-90868) is covered only after failure of at least two antidepressants.

The development of this guideline note was informed by a HERC [coverage guidance](#). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 103, BONE ANCHORED HEARING AIDS**

*Lines 311,444*

Bone anchored hearing aids (BAHA, CPT 69714, 69715) are included on these lines when the following criteria are met:

- A) The patient is aged 5-20 years for implanted bone anchored hearing aids; headband mounted BAHA devices may be used for children under age 5
- B) Treatment is for unilateral severe to profound hearing loss when the contralateral ear has normal hearing with or without a hearing aid
- C) Traditional air amplification hearing aids and contralateral routing of signal (CROS) hearing aid systems are not indicated or have been tried and are found to be not effective
- D) Implantation is unilateral.

Use of BAHA for treatment of tinnitus is not covered

**GUIDELINE NOTE 104, VISCOSUPPLEMENTATION OF THE KNEE**

*Lines 430,461*

CPT 20610 and 20611 are included on these lines only for interventions other than viscosupplementation for osteoarthritis of the knee.

The development of this guideline note was informed by a HERC [coverage guidance](#). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 105, MEDIASTITIS**

*Lines 285,655*

ICD-10-CM J98.51 (Mediastinitis) is included on Line 285 for acute mediastinitis and on Line 655 for chronic or fibrosing mediastinitis.

**GUIDELINE NOTE 106, PREVENTIVE SERVICES**

*Lines 3,619*

Included on Line 3 are the following preventive services:

- A) US Preventive Services Task Force (USPSTF) "A" and "B" Recommendations in effect and issued prior to January 1, 2017.
  - 1) <http://www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/>
  - 2) USPSTF "D" recommendations are not included on this line or any other line of the Prioritized List.
- B) American Academy of Pediatrics (AAP) Bright Futures Guidelines:
  - 1) <http://brightfutures.aap.org>. Periodicity schedule available at [http://www.aap.org/en-us/professional-resources/practice-support/Periodicity/Periodicity%20Schedule\\_FINAL.pdf](http://www.aap.org/en-us/professional-resources/practice-support/Periodicity/Periodicity%20Schedule_FINAL.pdf).
  - 2) Screening for lead levels is defined as blood lead level testing and is indicated for Medicaid populations at 12 and 24 months. In addition, blood lead level screening of any child between ages 24 and 72 months with no record of a previous blood lead screening test is indicated.
- C) Health Resources and Services Administration (HRSA) Women's Preventive Services - Required Health Plan Coverage Guidelines as retrieved from <http://www.hrsa.gov/womensguidelines/> on 1/1/2017.
- D) Immunizations as recommended by the Advisory Committee on Immunization Practices (ACIP):  
<http://www.cdc.gov/vaccines/schedules/hcp/index.html>

Colorectal cancer screening is included on Line 3 for average-risk adults aged 50 to 75, using one of the following screening programs:

- A) Colonoscopy every 10 years
- B) Flexible sigmoidoscopy every 5 years
- C) Fecal immunochemical test (FIT) every year
- D) Guaiac-based fecal occult blood test (gFOBT) every year



#### GUIDELINE NOTE 106, PREVENTIVE SERVICES (CONT'D)

Colorectal cancer screening for average-risk adults aged 76 to 85 is covered only for those who

- A) Are healthy enough to undergo treatment if colorectal cancer is detected, and
- B) Do not have comorbid conditions that would significantly limit their life expectancy.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

#### GUIDELINE NOTE 107, HYPERBARIC OXYGEN

Line 332

A course of hyperbaric oxygen treatment is included on this line subject to the following limitations:

- Codes appearing on this line from ICD-10-CM E08-E13 are included only when they are diabetic wound ulcers of the lower extremities which are Wagner grade 3 or higher (that is, involving bone or gangrenous) and show no measurable signs of healing after 30 days of adequate standard wound therapies including arterial assessment. Courses of treatment for wounds or ulcers are limited to 30 days after the initial treatment; additional 30 day treatment courses are only covered for patients with incomplete wound/infection resolution AND measurable signs of healing
- ICD-10-CM M27.2 is included on this line for osteoradionecrosis of the jaw only
- ICD-10-CM O08.0 and M60.0 are included on this line only if the infection is a necrotizing soft-tissue infection
- ICD-10-CM S07, S17, S38, S47.1, S47.2, S47.9, S57, S67, S77, S87, S97, T79.A are included on this line only for posttraumatic crush injury of Gustilo type III B and C
- ICD-10-CM T66.XXXA-T66.XXXD and L59.8 are included on this line only for osteoradionecrosis and soft tissue radiation injury
- ICD-10-CM T86.82, T82.898, T82.9, T83.89, T83.9, T84.89, T84.9, T85.89, T85.9 are included on this line only for compromised myocutaneous flaps

#### GUIDELINE NOTE 108, CONTINUOUS GLUCOSE MONITORING

Line 8

Real-time continuous glucose monitoring (CGM) is included on Line 8 for:

- A) Adults with type 1 diabetes mellitus not on insulin pump management:
  - 1) Who have received or will receive diabetes education specific to the use of CGM AND
  - 2) Who have used the device for at least 50% of the time at their first follow-up visit AND
  - 3) Who have baseline HbA1c levels greater than or equal to 8.0%, frequent or severe hypoglycemia, or impaired awareness of hypoglycemia (including presence of these conditions prior to initiation of CGM).
- B) Adults with type 1 diabetes on insulin pump management (including the CGM-enabled insulin pump):
  - 1) Who have received or will receive diabetes education specific to the use of CGM AND
  - 2) Who have used the device for at least 50% of the time at their first follow-up visit.
- C) Women with type 1 diabetes who are pregnant or who plan to become pregnant within six months without regard to HbA1c levels.
- D) Children and adolescents under age 21 with type 1 diabetes:
  - 1) Who have received or will receive diabetes education specific to the use of CGM AND
  - 2) Who have used the device for at least 50% of the time at their first follow-up visit.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

#### GUIDELINE NOTE 109, VERTEBROPLASTY, KYPHOPLASTY, AND SACROPLASTY

Line 476

Vertebroplasty and kyphoplasty are not included on this line (or any other line) for the treatment of routine osteoporotic compression fractures.

Vertebroplasty and kyphoplasty are only included on this line for the treatment of vertebral osteoporotic compression fractures when they are considered non-routine and meet all of the following conditions:

- A) The patient is hospitalized under inpatient status due to pain that is primarily related to a well-documented acute fracture, and
- B) The severity of the pain prevents unassisted ambulation, and
- C) The pain is not adequately controlled with oral or transcutaneous medication, and
- D) The patient must have failed an appropriate trial of conservative management.

Sacroplasty is not included on these or any lines of the Prioritized List for coverage consideration.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

#### GUIDELINE NOTE 110, CHRONIC PELVIC INFLAMMATORY CONDITIONS

Lines 51,529

Chronic pelvic inflammatory conditions (ICD-10-CM N70.91-N70.93, N71.9, N73.2, N73.4, N73.5, N73.8, N73.9, N74) are included only on Line 529; acute conditions are included on Line 51.



**GUIDELINE NOTE 111, INTRA-AORTIC BALLOON PUMPS**

Line 69

Intra-aortic balloon pumps (CPT 33967-33974) are included on this line only for use in cardiogenic shock.

**GUIDELINE NOTE 112, LUNG VOLUME REDUCTION SURGERY**

Line 283

Lung volume reduction surgery (LVRS, CPT 32491, 32672) is included on Line 283 only for treatment of patients with radiological evidence of severe bilateral upper lobe predominant emphysema (ICD-10-CM J43.9) and all of the following:

- A) BMI  $\leq 31.1$  kg/m<sup>2</sup> (men) or  $\leq 32.3$  kg/m<sup>2</sup> (women)
- B) Stable with  $\leq 20$  mg prednisone (or equivalent) dose a day
- C) Pulmonary function testing showing
  - 1) Forced expiratory volume in one second (FEV<sub>1</sub>)  $\leq 45\%$  predicted and, if age 70 or older, FEV<sub>1</sub>  $\geq 15\%$  predicted value
  - 2) Total lung capacity (TLC)  $\geq 100\%$  predicted post-bronchodilator
  - 3) Residual volume (RV)  $\geq 150\%$  predicted post-bronchodilator
- D) PCO<sub>2</sub>  $\leq 60$  mm Hg (PCO<sub>2</sub>  $\leq 55$  mm Hg if 1-mile above sea level)
- E) PO<sub>2</sub>  $\geq 45$  mm Hg on room air (PO<sub>2</sub>  $\geq 30$  mm Hg if 1-mile above sea level)
- F) Post-rehabilitation 6-min walk of  $\geq 140$  m
- G) Non-smoking and abstinence from all nicotine products for 6 months prior to surgery, as shown by negative cotinine levels at least 6 months apart, with the second test within 1 month of the surgery date.

The procedure must be performed at an approved facility (1) certified by the Joint Commission on Accreditation of Healthcare Organizations (Joint Commission) under the LVRS Disease Specific Care Certification Program or (2) approved as Medicare lung or heart-lung transplantation hospitals. The patient must have approval for surgery by pulmonary physician, thoracic surgeon, and anesthesiologist post-rehabilitation. The patient must have approval for surgery by cardiologist if any of the following are present: unstable angina; left-ventricular ejection fraction (LVEF) cannot be estimated from the echocardiogram; LVEF  $<45\%$ ; dobutamine-radiolabeled cardiac scan indicates coronary artery disease or ventricular dysfunction; arrhythmia ( $>5$  premature ventricular contractions per minute; cardiac rhythm other than sinus; premature ventricular contractions on EKG at rest).

**GUIDELINE NOTE 113, DISEASES OF LIPS**

Lines 206,580

ICD-10-CM K13.0 (Diseases of lips) is included on Line 206 only for treatment of abscess or cellulitis of the lips. All other diagnoses coded using K13.0 are included on Line 580.

**GUIDELINE NOTE 114, FEMOROACETABULAR IMPINGEMENT SYNDROME**

Line 356

ICD-10-CM M25.85 (Other specified joint disorders, hip), M24.15 (Other articular cartilage disorders, hip) and M76.2 (Iliac crest spur) pair with CPT codes 29914-29916 (Arthroscopy, hip, surgical) and are included on Line 356 only for the diagnosis and treatment of femoroacetabular impingement syndrome.

Surgery for femoroacetabular impingement syndrome is included on this line only for patients who meet all of the following criteria:

- A) Adult patients, or adolescent patients who are skeletally mature with documented closure of growth plates; and
- B) Other sources of pain have been ruled out (e.g., lumbar spine pathology, SI joint dysfunction, sports hernia); and
- C) Pain unresponsive to physical therapy and other non-surgical management and conservative treatments (e.g., restricted activity, cortisone injections, nonsteroidal anti-inflammatory drugs) of at least three months duration, or conservative therapy is contraindicated; and
- D) Moderate-to-severe persistent hip or groin pain that significantly limits activity and is worsened by flexion activities (e.g., squatting or prolonged sitting); and
- E) Positive impingement sign (i.e., sudden pain on 90 degree hip flexion with adduction and internal rotation or extension and external rotation); and
- F) Radiographic confirmation of FAI (e.g., pistol-grip deformity, alpha angle greater than 50 degrees, coxa profunda, and/or acetabular retroversion); and
- G) Do not have advanced osteoarthritis (i.e., Tönnis grade 2 or 3) and/or severe cartilage damage (i.e., Outerbridge grade III or IV).

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 115, EXTRACORPOREAL PHOTOPHERESIS**

Lines 158,313

Extracorporeal photopheresis (CPT 36522) is included on Line 158 for treatment of chronic T-cell lymphoma (ICD-10-CM C84.0 and C84.1) which is:

- A) stage III or IVA
- B) erythrodermic



**GUIDELINE NOTE 115, EXTRACORPOREAL PHOTOPHERESIS (CONT'D)**

- C) not responsive to other therapy

Extracorporeal photopheresis (CPT 36522) is included on Line 313 for treatment of chronic graft-versus-host disease (ICD-10-CM T86.0) which

- A) is steroid refractory, steroid dependent or the patient is unable to tolerate corticosteroid therapy  
B) primarily affects skin or mucosal membranes (mouth and/or eye disease)

**GUIDELINE NOTE 116, INTRAOCULAR STEROID TREATMENTS**

*Lines 96,360,439*

Intraocular steroid treatments (CPT 67027, 67028) are included on Line 360 for pairing with uveitis (ICD-10-CM H30.0, H30.1, H30.89, H30.9, H44.11) when the following conditions are met: uveitis is chronic, non-infectious, and there has been appropriate trial and failure, or intolerance of therapy, with local and systemic corticosteroids and/or immunosuppressive agents.

Intraocular steroid treatments (CPT 67027, 67028) are included on Line 96 for treating chronic diabetic macular edema (ICD-10-CM E11.311) only when there has been insufficient response to anti-VEGF therapies, and only when FDA approved treatments are utilized.

Intraocular steroid treatments (CPT 67027, 67028) are only included on Line 439 for treatment of macular edema due to:

- A) Central retinal vein occlusion (ICD-10-CM H34.81) in those individuals who have failed anti-VEGF therapy.  
B) Branch retinal vein occlusion (ICD-10-CM H34.83) when treatment with laser photocoagulation has not been beneficial, or treatment with laser photocoagulation is not considered suitable because of the extent of macular hemorrhage in those individuals who have failed anti-VEGF therapy.

**GUIDELINE NOTE 117, REMOVAL OF TORI AND EXCISION OF HYPERPLASTIC TISSUE**

*Line 451*

D7472 and D7473, and D7970 are included on this line only when used in conjunction with making a prosthesis.

**GUIDELINE NOTE 118, OBSTRUCTIVE SLEEP APNEA DIAGNOSIS AND TREATMENT FOR CHILDREN**

*Line 203*

Obstructive sleep apnea (OSA) in children (18 or younger) must be diagnosed by

- A) nocturnal polysomnography with an AHI >5 episodes/h or AHI>1 episodes/h with history and exam consistent with OSA, OR  
B) nocturnal pulse oximetry with 3 or more SpO2 drops <90% and 3 or more clusters of desaturation events, or alternatives desaturation (>3%) index >3.5 episodes/h, OR  
C) use of a validated questionnaire (such as the Pediatric Sleep Questionnaire or OSA 18), OR  
D) consultation with a sleep medicine specialist.

Polysomnography and/or consultation with a sleep medicine specialist to support the diagnosis of OSA and/or to identify perioperative risk is recommended for

- A) high risk children (i.e. children with cranio-facial abnormalities, neuromuscular disorders, Down syndrome, etc.)  
B) children with equivocal indications for adenotonsillectomy (such as discordance between tonsillar size on physical examination and the reported severity of sleep-disordered breathing),  
C) children younger than three years of age

Adenotonsillectomy is an appropriate first line treatment for children with OSA. Weight loss is recommended in addition to other therapy in patients who are overweight or obese. Adenoidectomy without tonsillectomy is only covered when a child with OSA has previously had a tonsillectomy, when tonsillectomy is contraindicated, or when tonsillar hypertrophy is not present. More complex surgical treatments are only included on this line for children with craniofacial anomalies.

Intranasal corticosteroids are an option for children with mild OSA in whom adenotonsillectomy is contraindicated or for mild postoperative OSA.

CPAP is covered for a 3 month trial for children through age 18 who have

- A) undergone surgery or are not candidates for surgery, AND  
B) have documented residual sleep apnea symptoms (sleep disruption and/or significant desaturations) with residual daytime symptoms (daytime sleepiness or behavior problems)

CPAP will be covered for children through age 18 on an ongoing basis if:

- There is documentation of improvement in sleep disruption and daytime sleepiness and behavior problems with CPAP use
- Annual re-evaluation for CPAP demonstrates ongoing clinical benefit and compliance with use, defined as use of CPAP for at least four hours per night on 70% of the nights in a consecutive 30 day period



#### **GUIDELINE NOTE 119, CAROTID ENDARTERECTOMY**

*Line 414*

Carotid endarterectomy is included on Line 414 for patients in the following groups:

- Symptomatic<sup>1</sup> with 70-99% carotid artery stenosis but without near occlusion.
- Symptomatic with 50 – 69% stenosis despite optimal medical management
- Asymptomatic with at least 60% stenosis only for those who do not tolerate (or have contraindications to) best current medical therapy

Carotid endarterectomy is not included on Line 414 for patients in the following groups:

- Patients with near occlusion
- Symptomatic<sup>1</sup> patients with less than 50% carotid stenosis

<sup>1</sup>Symptomatic patients are those who have had a recent transient ischemic attack or ischemic stroke.

The development of this guideline note was informed by a HERC [coverage guidance](#). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

#### **GUIDELINE NOTE 120, PEDIATRIC TRIGGER THUMB**

*Line 376*

ICD-10-CM M65.31 is included on Line 376 for treatment of pediatric trigger thumb only. Surgical treatment should be reserved for trigger thumb that does not spontaneously resolve within 48 months of diagnosis. Immediate surgery may be considered for bilateral trigger thumb or trigger thumb with locking symptoms.

#### **GUIDELINE NOTE 121, CONCUSSION AND POST CONCUSSION SYNDROME**

*Lines 92,202,609*

ICD-10-CM S06.0X0, S06.2X0 and S06.300 are included on Line 92 only for concussions with symptoms that persist for more than 7 days but less than 3 months; otherwise, these diagnoses are included on Line 609. When concussion symptoms last for more than 3 months, the diagnosis of post-concussive syndrome (ICD-10-CM F07.81) should be used, which is included on Line 202.

#### **GUIDELINE NOTE 122, ORAL HEALTH RISK ASSESSMENT IN MEDICAL SETTINGS**

*Line 3*

D0191 is limited to children under age 6 and requires an additional specific oral health risk assessment using a standardized tool, such as AAP Bright Futures, and should be performed by a provider who has successfully completed an approved training program (such as First Tooth or Smiles for Life).

#### **GUIDELINE NOTE 123, DENTAL FILLINGS FOR POSTERIOR TEETH**

*Line 343*

For dental fillings in posterior teeth, amalgam is preferred for extensive restorations. If amalgam is unavailable or contraindicated, composite is acceptable.

#### **GUIDELINE NOTE 124, ALCOHOL SEPTAL ABLATION**

*Line 99*

Alcohol septal ablation (CPT 93583) is included on Line 99 only for adult patients with hypertrophic cardiomyopathy when all of the following conditions are met:

- A) Severe heart failure symptoms (New York Heart Association [NYHA] class III or IV)
- B) Severe symptoms refractory to optimal medical management
- C) LVOT obstruction is present
- D) Surgery is contraindicated or has unacceptable risk due to serious comorbidities or advanced age.
- E) No concomitant disease is present that independently warrants surgical correction in whom surgical myectomy can be performed as part of the operation.
- F) The ablation is performed at an experienced center

#### **GUIDELINE NOTE 125, CAROTID ARTERY STENTING**

*Lines 317,414*

Carotid artery stenting (CPT 37215-37217) is included on Lines 317 and 414 for patients who have not had a disabling stroke (modified Rankin scale  $\geq 3$ ) AND



**GUIDELINE NOTE 125, CAROTID ARTERY STENTING (CONT'D)**

- A) who are at high risk for complications during carotid endarterectomy (CEA) due to significant comorbidities and/or anatomic risk factors (i.e., recurrent stenosis and/or previous radical neck dissection) and who also have symptomatic (recent transient ischemic attack or ischemic stroke) carotid artery stenosis >50% OR
- B) who are at high risk for complications during CEA due to significant comorbidities and/or anatomic risk factors and have asymptomatic carotid artery stenosis ≥80% only if best current medical therapy is not tolerated or contraindicated.

**GUIDELINE NOTE 126, APPLIED BEHAVIOR ANALYSIS INTERVENTIONS FOR SELF-INJURIOUS BEHAVIOR**

*Line 436*

Targeted ABA-based interventions towards self-injurious problem behaviors are included on this line when meeting criteria as defined in Guideline Note 75 APPLIED BEHAVIOR ANALYSIS FOR AUTISM SPECTRUM DISORDER.

**GUIDELINE NOTE 127, GENDER DYSPHORIA**

*Line 312*

Hormone treatment with GnRH analogues for delaying the onset of puberty and/or continued pubertal development is included on this line for gender questioning children and adolescents. This therapy should be initiated at the first physical changes of puberty, confirmed by pubertal levels of estradiol or testosterone, but no earlier than Tanner stages 2-3. Prior to initiation of puberty suppression therapy, adolescents must fulfill eligibility and readiness criteria and must have a comprehensive mental health evaluation. Ongoing psychological care is strongly encouraged for continued puberty suppression therapy.

Cross-sex hormone therapy is included on this line for treatment of adolescents and adults with gender dysphoria who meet appropriate eligibility and readiness criteria. To qualify for cross-sex hormone therapy, the patient must:

- A) have persistent, well-documented gender dysphoria
- B) have the capacity to make a fully informed decision and to give consent for treatment
- C) have any significant medical or mental health concerns reasonably well controlled
- D) have a comprehensive mental health evaluation provided in accordance with Version 7 of the World Professional Association for Transgender Health (WPATH) Standards of Care ([www.wpath.org](http://www.wpath.org)).

Sex reassignment surgery is included for patients who are sufficiently physically fit and meet eligibility criteria. To qualify for surgery, the patient must:

- A) have persistent, well documented gender dysphoria
- B) for genital surgeries, have completed twelve months of continuous hormone therapy as appropriate to the member's gender goals unless hormones are not clinically indicated for the individual
- C) have completed twelve months of living in a gender role that is congruent with their gender identity unless a medical and a mental health professional both determine that this requirement is not safe for the patient
- D) have the capacity to make a fully informed decision and to give consent for treatment
- E) have any significant medical or mental health concerns reasonably well controlled
- F) for breast/chest surgeries, have one referral from a mental health professional provided in accordance with version 7 of the WPATH Standards of Care.
- G) For genital surgeries, have two referrals from mental health professionals provided in accordance with version 7 of the WPATH Standards of Care.

Electrolysis (CPT 17380) and laser hair removal (CPT 17110, 17111) are only included on this line as part of pre-surgical preparation for chest or genital surgical procedures also included on this line. These procedures are not included on this line for facial or other cosmetic procedures or as pre-surgical preparation for a procedure not included on this line.

Mammoplasty (CPT 19316, 19324-19325, 19340, 19342, 19350) is only included on this line when 12 continuous months of hormonal (estrogen) therapy has failed to result in breast tissue growth of Tanner Stage 5 on the puberty scale OR there is any contraindication to, intolerance of or patient refusal of hormonal therapy.

Revisions to surgeries for the treatment of gender dysphoria are only covered in cases where the revision is required to address complications of the surgery (wound dehiscence, fistula, chronic pain directly related to the surgery, etc.). Revisions are not covered solely for cosmetic issues.

Pelvic physical therapy (CPT 97001, 97001, 97110, 97140, and 97530) is included on this line only for pre- and post-operative therapy related to genital surgeries also included on this line and as limited in Guideline Note 6 REHABILITATIVE AND HABILITATIVE THERAPIES.

**GUIDELINE NOTE 128, FOREIGN BODIES IN THE GI TRACT**

*Lines 41, 498*

ICD-10-CM T18.2XXD, T18.3XXD, T18.4XXD, T18.5XXD, T18.8XXD, T18.9XXD) are included on Line 41 only when hazardous objects are involved that are likely to cause perforation (e.g. sharp objects >2 inches, neodymium magnets, button batteries) or obstruction.



**GUIDELINE NOTE 129, FECAL INCONTINENCE**

*Lines 71,526*

ICD-10-CM R15.9 (Full incontinence of feces) is included on Line 71 only for supportive equipment (e.g. diapers, gloves). Surgical treatment for fecal incontinence is included on Line 526 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS

**GUIDELINE NOTE 130, BLEPHAROPLASTY**

*Line 469*

Blepharoplasty is covered when 1) visual fields demonstrate an absolute superior defect to within 15 degrees of fixation, 2) upper eyelid position contributes to difficulty tolerating a prosthesis in an anophthalmic socket, 3) essential blepharospasm or hemifacial spasm is present, OR 4) when there is significant ptosis in the downgaze reading position.

**GUIDELINE NOTE 131, HYPOTONY**

*Lines 285,652*

ICD-10-CM H44.40-H44.439 (hypotony of the eye) are only included on Line 285 when resulting from a complication of a procedure. Non-procedure related cases are included on Line 652.

**GUIDELINE NOTE 132, ACNE CONGLOBATA**

*Line 373*

Acne conglobata is only included on Line 373 if it involves recurrent abscesses or communicating sinuses.

**GUIDELINE NOTE 133, ACUTE PERIPHERAL MOTOR AND DIGITAL NERVE INJURY**

*Lines 208,425,507,534*

Repair of acute (<6 months) peripheral nerve injuries are included on Lines 208 and 425. Non-surgical medical care of these injuries are included on Line 507. Surgical repair of chronic nerve injuries are included on Line 534.

**GUIDELINE NOTE 134, NEONATAL NASOLACRIMAL DUCT OBSTRUCTION**

*Lines 393,508*

Probing of nasolacrimal duct (CPT 68810-68840) is included on Line 393 only for children 12 months of age and older who have failed conservative management (e.g. topical antibiotics, Crigler massage) and for children younger than 12 months of age with multiple episodes of purulent infections.

**GUIDELINE NOTE 135, FIBROMYALGIA**

*Line 528*

Fibromyalgia (ICD-10-CM M79.7) treatment should consist of a multi-modal approach, which should include two of more of the following:

- A) medications other than opioids
- B) exercise advice/programs
- C) cognitive behavioral therapy.

Care should be provided in the primary care setting. Referrals to specialists are generally not required. Use of opioids should be avoided due to evidence of harm in this condition.

**GUIDELINE NOTE 136, COLLAPSED VERTEBRA**

*Lines 150,476*

Diagnosis codes appearing on this line for collapsed vertebra (in the ICD-10-CM M48.5 series) are included on Line 150 for a fracture that qualified for trauma system entry or a fracture with spinal cord injury.

**GUIDELINE NOTE 137, BENIGN BONE TUMORS**

*Lines 400,556*

Treatment of benign conditions of joints (ICD-10-CM D18.09 synovial hemangioma, D17.79 lipoma arborescens, D48.1 tenosynovial giant cell tumor, M67.8 synovial chondromatosis and M12.2 villonodular synovitis) are included on Line 400 for those conditions only when there are significant functional problems of the joint due to size, location, or progressiveness of the disease. Treatment of all other benign joint conditions are included on Line 556.

Treatment of benign tumors of bones (ICD-10-CM D16.00-D16.9, K09.0, K09.1, M27.1, M27.40, M27.49, M85.40-M85.69) are included on Line 400 for those neoplasms associated with pathologic fractures, at high risk of fracture, or which cause function problems

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**GUIDELINE NOTE 137, BENIGN BONE TUMORS (CONT'D)**

including impeding joint function due to size, causing nerve compression, have malignant potential or are considered precancerous. Treatment of all other benign bone tumors are included on Line 556

**GUIDELINE NOTE 138, OBSTRUCTIVE AND REFLUX UROPATHY**

*Line 21*

ICD-10-CM N13.9 (Obstructive and reflux uropathy unspecified) appears on this line for pediatric populations only.

**GUIDELINE NOTE 139, FRENOTOMY FOR TONGUE-TIE IN NEWBORNS**

*Lines 18,593*

Ankyloglossia (ICD-10-CM Q38.1 is included on Line 18 for pairing with frenotomy (CPT 41010, CDT D7960) only when it interferes with breastfeeding. Otherwise, Q38.1 and CPT 41010 are included on Line 593.

**GUIDELINE NOTE 140, BREASTFEEDING SUPPORT AND SUPPLIES**

*Line 3*

Breast pumps and supplies are covered for postpartum women when a pump is necessary to establish or maintain milk production in order to maximize availability of breast milk to the baby.

For cases in which there is a medical indication for breast pumps, the pumps should be supplied whenever possible within 24 hours to allow for continued milk production.

Lactation support services (including education and counseling by trained providers) are covered for pregnant and postpartum women (for six months postpartum).

**GUIDELINE NOTE 141, LARYNGEAL STENOSIS OR PARALYSIS; DYSPHONIA**

*Lines 66,516*

Laryngeal and vocal cord paralysis (ICD-10-CM J38.01 and J38.02) are included on line Line 66 if associated with recurrent aspiration pneumonia (unilateral or bilateral) or airway obstruction (bilateral). Vocal cord paralysis is included on line 70 for children 18 and under with dysphonia or dysphagia persisting for at least twelve months. Treatment of hoarseness and dysphonia in adults are included only on Line 516. Laryngeal stenosis (ICD-10-CM J38.6) is included on Line 66 only if it causes airway obstruction; otherwise it is included on Line 516.

**GUIDELINE NOTE 142, STEREOTACTIC BODY RADIATION THERAPY**

*Line 263*

Stereotactic body radiation therapy (CPT 32701, 77373, 77435) is included on Line 263 only for early stage non-small cell lung cancer in medically inoperable patients.

**GUIDELINE NOTE 143, TREATMENT OF UNILATERAL HEARING LOSS**

*Lines 311,444*

Unilateral hearing loss treatment is Included on these lines only for children aged 20 and younger with the following conditions:

1. For mild to moderate sensorineural unilateral hearing loss (defined as 26-70 dB hearing loss at 500, 1000 and 2000 Hz), first line intervention should be a conventional hearing aid, with second line therapy being contralateral routing of signal (CROS) system
2. For severe to profound unilateral sensorineural hearing loss (defined as 71 dB hearing loss or greater at 500, 1000 and 2000 Hz), first line therapy should be a contralateral routing of signal (CROS) system with second line therapy being a bone anchored hearing aid (BAHA). BAHA SoftBand therapy may be first line therapy for children under age 5 or patients with severe ear deformities (e.g. microstia, severe canal atresia).

Cochlear implants are not included on these lines for unilateral hearing loss per Guideline Note 31 COCHLEAR IMPLANTATION.

**GUIDELINE NOTE 144, PROTON PUMP INHIBITOR THERAPY FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD)**

*Lines 314,380,511*

Short term treatment (up to 8 weeks) of GERD without Barrett's (ICD-10-CM K20.8, K20.9, K21.0, K21.9) with proton pump inhibitor therapy is included on Line 380.

Long term proton pump inhibitor therapy is included on Line 380 for Barrett's esophagus (ICD-10-CM K22.70). Long term treatment is included on Line 511 and on Line 314 for Barrett's esophagus with dysplasia (ICD-10-CM K22.71).



**GUIDELINE NOTE 145, TREATMENTS FOR BENIGN PROSTATE ENLARGEMENT WITH LOWER URINARY TRACT SYMPTOMS**

*Line 327*

For men with lower urinary tract symptoms (LUTS) due to benign prostate enlargement, coverage of surgical procedures is recommended only if symptoms are severe, and if drug treatment and conservative management options have been unsuccessful or are not appropriate.

The following interventions for benign prostate enlargement are not included on Line 327 due to lack of evidence of effectiveness:

- Botulinum toxin
- HIFU (High Intensity Focused Ultrasound)
- TEAP (Transurethral Ethanol Ablation of the Prostate)
- Prostatic urethral lifts
- Laser coagulation (for example, VLAP/ILC)
- Prostatic artery embolization

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 146, ABLATION PROCEDURES FOR ATRIAL FIBRILLATION**

*Line 347*

AV nodal ablation (CPT 33250, 33251, 33261, 93650) pairs with atrial fibrillation (ICD-10-CM I48.0, I48.1, I48.2, I48.91) only for patients with inadequate ventricular rate control resulting in symptoms, left ventricular systolic dysfunction or substantial risk of left ventricular systolic dysfunction, when pharmacological therapy for rate control is ineffective or not tolerated

Transcatheter pulmonary vein isolation (93656-93657) pairs with atrial fibrillation (ICD-10-CM I48.0, I48.1, I48.2, I48.91) only for patients who remain symptomatic from atrial fibrillation despite rate control medications and antiarrhythmic medications.

Surgical ablation (pulmonary vein isolation or Maze procedure) (CPT 33254-33259, 33265, 33266) only pairs with atrial fibrillation (ICD-10-CM I48.0, I48.1, I48.2, I48.91) at the time of other cardiac surgery for patients who remain symptomatic despite rate control medications.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 147, IVC FILTERS FOR ACTIVE PULMONARY EMBOLISM (PE)/DEEP VEIN THROMBOSIS (DVT)**

*Lines 1,79,214,280,285*

Inferior vena cava (IVC) filter placement (CPT 37191) is included on these lines for patients with active deep vein thrombosis/pulmonary embolism (DVT/PE) for which anticoagulation is contraindicated. IVC filter placement is not included on these lines for patients with DVT who are candidates for anticoagulation.

Retrieval of removable IVC filters (CPT 37193) is included on these lines when the benefits of removal outweigh the harms.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 148, BIOMARKER TESTS OF CANCER TISSUE**

*Lines 157,184,191,230,263,271,329*

The use of multiple molecular testing to select targeted cancer therapy (CPT 81504) is included on the Services recommended for non-coverage table.

For breast cancer, Oncotype Dx testing (CPT 81519, HCPCS S3854) is included on Line 191 only for early stage breast cancer when used to guide adjuvant chemotherapy treatment decisions for women who are lymph node negative. Oncotype Dx is not included on this line for lymph node-positive breast cancer. Mammaprint, ImmunoHistoChemistry 4 (IHC4), and Mammostrat for breast cancer are included on the Services recommended for noncoverage table.

For melanoma, BRAF gene mutation testing (CPT 81210) is included on Line 230.

For lung cancer, epidermal growth factor receptor (EGFR) gene mutation testing (CPT 81235) is included on Line 263 only for non-small cell lung cancer. KRAS gene mutation testing (CPT 81275) is not included on this line.

For colorectal cancer, KRAS gene mutation testing (CPT 81275) is included on Line 157. BRAF (CPT 81210) and Oncotype DX are not included on this line. Microsatellite instability (MSI) is included on the Services recommended for noncoverage table.

For bladder cancer, Urovysion testing is included on Services recommended for noncoverage table.



**GUIDELINE NOTE 148, BIOMARKER TESTS OF CANCER TISSUE (CONT'D)**

For prostate cancer, Oncotype DX is not included on Line 329 and Prolaris is included on the Services recommended for noncoverage table.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 149, SCLEROTHERAPY OF FLUID COLLECTIONS**

*Lines 168,225,293,421,422,478,542,554,564,590,601,628*

Sclerotherapy for fluid collections (CPT 49185) is included on these lines only for the treatment of cysts, seromas or lymphoceles which are causing bleeding, infection, severe pain, organ torsion, or organ dysfunction.

**GUIDELINE NOTE 150, FETAL MRI**

*Line 1*

Fetal MRI (CPT 74712-74713) is included on this line only when all of the following conditions are met:

- A) Abnormalities are found on fetal ultrasound performed by an experienced sonologist which cannot be adequately further evaluated by 2D or 3D ultrasound
- B) The information obtained by fetal MRI is necessary for decisions about fetal or neonatal therapy, delivery planning, or to advise a family about prognosis
- C) The fetus is 18 weeks gestational age or older
- D) The MRI is performed and interpreted at a center with technicians and radiologists who are either trained or highly experienced in fetal MRI and which has appropriate MRI equipment, with a minimum of a 1.5 Tesla magnet.

**GUIDELINE NOTE 151, CARDIAC TRANSPLANT GENETIC TESTING FOR TRANSPLANT REJECTION**

*Lines 241,264*

Genetic testing for cardiac transplant rejection (CPT 81595) is included on these lines only for patients at least 1 year post transplant who are without clinical signs of rejection.

**GUIDELINE NOTE 152, UNSPECIFIED CONDUCT DISORDER**

*Lines 419,477*

ICD-10-CM F91.9 (Conduct disorder, unspecified) is included on Line 419 only for children ages 5 and younger who cannot be diagnosed with a more specific mental health diagnosis. This diagnosis is included on Line 477 for older children and adolescents.

**GUIDELINE NOTE 153, PLANNED OUT-OF-HOSPITAL BIRTH**

*Lines 1,2*

Planned out-of-hospital birth is included on these lines when appropriate risk assessments are performed, and the consultation and transfer criteria are followed, and no high risk coverage exclusion criteria exist. Risk assessment should be done initially when planning the location of birth, and updated throughout pregnancy, labor, and delivery to determine if out-of-hospital birth is still appropriate.

The clinical and/or diagnostic assessment of each criterion, with the exception of those marked with an asterisk, is necessary for planned out-of-hospital birth to be included on these lines. (Criteria marked with an asterisks may not be known or not be pertinent if there is no clinical indication for concern and additional diagnostic testing is not indicated.)

An ultrasound is required to rule out certain risk criteria (e.g. multiple gestation, placenta previa, and life threatening congenital anomalies). Certain risk criteria require serial measurements such as fundal height and blood pressure.

If a woman refuses a required clinical or diagnostic assessment, then ascertainment of her risk status is unknowable and she does not meet criteria for coverage for an out-of-hospital birth.

Documentation of continuing appropriate risk assessment and routine prenatal care is required.

High-risk coverage exclusion criteria:

*Complications in a previous pregnancy:*

- Maternal surgical history
- Cesarean section or other hysterotomy
  - Uterine rupture
  - Retained placenta requiring surgical removal
  - Fourth-degree laceration without satisfactory functional recovery



**GUIDELINE NOTE 153, PLANNED OUT-OF-HOSPITAL BIRTH (CONT'D)**

Maternal medical history

- Pre-eclampsia requiring preterm birth
- Eclampsia
- HELLP syndrome

Fetal and placental

- Unexplained stillbirth/neonatal death or previous death related to intrapartum difficulty
- Baby with neonatal encephalopathy
- Placental abruption with adverse outcome

*Complications of current pregnancy:*

Maternal

- Induction of labor
- Prelabor rupture of membranes > 24 hours
- Pre-existing chronic hypertension; Pregnancy-induced hypertension with diastolic blood pressure greater than or equal to 90 mmHg or systolic blood pressure greater than or equal to 140 mmHg on two consecutive readings taken at least 30 minutes apart
- Unknown group B strep carrier state
- Lack of informed consent on group B strep prophylaxis, if mother is Group B strep positive.
- Eclampsia or pre-eclampsia
- Anemia – hemoglobin less than 8.5 g/dL
- Thrombocytopenia (platelets <100,000)
- Thrombosis/thromboembolism or other maternal bleeding disorder\*
- Maternal mental illness requiring inpatient care\*
- Drug or alcohol use with high risk for adverse effects to fetal or maternal health
- Unknown, or positive, syphilis, HIV, or Hepatitis B status
- Current active infection of varicella at the time of labor; rubella infection anytime during pregnancy; active infection (outbreak) of genital herpes at the time of labor\*
- Refractory hyperemesis gravidarum\*
- Diabetes, type I or II, uncontrolled gestational diabetes, or gestational diabetes controlled with medication

Placental

- Low lying placenta within 2 cm or less of cervical os at term; placenta previa, vasa previa
- Placental abruption/abnormal bleeding
- Recurrent antepartum hemorrhage
- Uteroplacental insufficiency\*

Fetal

- Gestational age - preterm or postdates (defined as gestational age < 37 weeks + 0 days or > 41 weeks + 6 days)
- Multiple gestation
- Non-cephalic fetal presentation
- IUGR (defined as fetal weight less than fifth percentile using ethnically-appropriate growth tables, or concerning reduced growth velocity on ultrasound)\*
- Oligohydramnios or polyhydramnios\*
- Abnormal fetal heart rate/Doppler/surveillance studies
- Blood group incompatibility with atypical antibodies, or Rh sensitization
- Molar pregnancy

Transfer criteria:

If out-of-hospital birth is planned, certain intrapartum and postpartum complications may necessitate transfer to a hospital to meet coverage criteria. For these indications, an attempt should be made to transfer the mother and/or her newborn; however, imminent fetal delivery may delay or preclude actual transfer prior to birth.

*Maternal*

- Temperature  $\geq 38.0$  C
- Maternal infection requiring hospital treatment (e.g. endometritis or wound infection)
- Hemorrhage (hypovolemia, shock, need for transfusion)
- Retained placenta > 60 minutes
- Laceration requiring hospital repair (e.g., extensive vaginal, cervical or third- or fourth-degree trauma)
- Enlarging hematoma
- Bladder or rectal dysfunction

*Fetal and uterine*

- Repetitive or persistent abnormal fetal heart rate pattern
- Thick meconium staining of amniotic fluid



**GUIDELINE NOTE 153, PLANNED OUT-OF-HOSPITAL BIRTH (CONT'D)**

- Prolapsed umbilical cord
- Failure to progress (as defined by the American Congress of Obstetricians and Gynecologists, March 2014, found at <http://www.acog.org/Resources-And-Publications/Obstetric-Care-Consensus-Series/Safe-Prevention-of-the-Primary-Cesarean-Delivery>)/failure of head to engage in active labor
- Chorioamnionitis or other serious infection (including toxoplasmosis, rubella, CMV, HIV, etc.)
- Uterine rupture, inversion or prolapse

If the infant is delivered out-of-hospital, the following complications require transfer to a hospital for the out-of-hospital birth to meet coverage criteria:

- Low Apgar score (< 5 at 5 minutes, < 7 at 10 minutes)
- Weight less than 5th percentile for gestational age
- Unexpected significant or life-threatening congenital anomalies
- Respiratory or cardiac irregularities, cyanosis, pallor
- Temperature instability, fever, suspected infection or dehydration
- Hyperglycemia/hypoglycemia unresponsive to treatment
- Hypotonia, tremors, seizures, hyperirritability
- Excessive bruising, enlarging cephalohematoma, significant birth trauma
- Vomiting/diarrhea

Consultation criteria:

Certain high risk conditions require consultation (by a provider of maternity care who is credentialed to admit and manage pregnancies in a hospital) for coverage of a planned out-of-hospital birth to be recommended. These complications include (but are not limited to) patients with:

*Complications in a previous pregnancy:*

**Maternal**

- More than three first trimester spontaneous abortions, or more than one second trimester spontaneous abortion
- More than one preterm birth, or preterm birth less than 34 weeks 0 days in most recent pregnancy
- Pre-eclampsia, not requiring preterm birth
- Cervical insufficiency/prior cerclage
- Third degree laceration; fourth-degree laceration with satisfactory functional recovery
- Life-threatening congenital anomalies (unless fatal anomalies with nonresuscitation planned)
- Postpartum hemorrhage requiring additional pharmacologic treatment or blood transfusion
- Retained placenta requiring manual removal

**Fetal**

- Child with congenital and/or hereditary disorder
- Baby > 4.5 kg or 9 lbs 14 oz
- Shoulder dystocia, with or without fetal clavicular fracture
- Unexplained stillbirth/neonatal death or previous death unrelated to intrapartum difficulty
- Unresolved intrauterine growth restriction (IUGR) or small for gestational age (defined as fetal or birth weight less than fifth percentile using ethnically-appropriate growth tables)
- Blood group incompatibility, and/or Rh sensitization

*Complications of current pregnancy:*

**Maternal**

- Inadequate prenatal care (defined as less than five prenatal visits or care began in the third trimester)
- Body mass index at first prenatal visit of greater than 35 kg/m<sup>2</sup>
- History of maternal seizure disorder (excluding eclampsia)
- Gestational diabetes, diet-controlled
- Maternal mental illness with suspicion for psychosis or potential harm to self or infant under outpatient psychiatric care
- Maternal anemia with hemoglobin < 10.5 g/dL, unresponsive to treatment
- Third-degree laceration not requiring hospital repair
- Laparotomy during pregnancy

**Fetal**

- Fetal macrosomia (estimated weight >4.5 kg or 9 lbs 14 oz)
- Confirmed intrauterine death
- Family history of genetic/heritable disorders that would impact labor, delivery or newborn care

The development of this guideline note was informed by a HERC [coverage guidance](#). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.



**GUIDELINE NOTE 154, EAR DRUM REPAIR**

*Lines 311,444,473*

Repair of open wounds or perforations of the ear drum (codes included on these lines from ICD-10-CM H72, S09.2) are only included on Lines 311 and 444 when there is documented conductive hearing loss greater than or equal to 25dB persistent for more than three months. Otherwise, such repairs are included on Line 473 CHRONIC OTITIS MEDIA; OPEN WOUND OF EAR DRUM.

**GUIDELINE NOTE 155, ELECTRIC TUMOR TREATMENT FIELDS FOR GLIOBLASTOMA**

*Line 294*

Electric tumor treatment fields (codes HCPCS A4555 and E0766) are included on this line only when

- A) Used for the initial treatment of supratentorial glioblastoma
- B) Used in combination with temozolomide

Electric tumor treatment fields are not included on this line for recurrent glioblastoma or any other indication.

**GUIDELINE NOTE 156, ENCOUNTER FOR DESENSITIZATION TO ALLERGENS**

*Lines 9,103,124,223,313,530,531,550,559,566*

ICD-10-CM Z51.6 (Encounter for desensitization to allergens) is only included on these lines when used to treat a diagnosis appearing on a line above the current funding line (i.e. Lines 9, 103, 124, 223 and 313).

**GUIDELINE NOTE 157, WIGS**

*Line 422*

Wigs (HCPCS A9282) are covered only for hair loss due to chemotherapy or radiation therapy.

**GUIDELINE NOTE 158, HALLUX RIGIDUS**

*Lines 356,540*

Surgical treatment of hallux rigidus is included on Line 356 only for

- Stage 3 and 4 disease when paired with arthroplasty (CPT 28750), the Keller procedure (CPT 28292), or cheilectomy with implant (CPT 28291)
- Stage 2 disease when paired with cheilectomy (CPT 28289) and there is documentation that conservative therapy (e.g. injection, physical therapy, orthotics) has been tried and failed to adequately control symptoms.

Otherwise surgical treatment of this diagnosis is included on Line 540.

**GUIDELINE NOTE 159, SMOKING AND SURGICAL TREATMENT OF ERECTILE DYSFUNCTION**

*Line 521*

Surgical treatment of erectile dysfunction is only included on this line when patients are non-smoking and abstinent from all nicotine products for 6 months prior to surgery, as shown by negative cotinine levels at least 6 months apart, with the second test within 1 month of the surgery date.

**GUIDELINE NOTE 160, CONGENITAL MUSCULAR TORTICOLLIS**

*Line 401*

Congenital muscular torticollis (ICD-10-CM Q68.0 Congenital deformity of sternocleidomastoid muscle) is paired with physical therapy on this line only in the following circumstances:

- 1) The patient is a child aged 2 years or younger
- 2) For patients with deficits of passive rotation of the neck of < 10 degrees, one therapy visit is included for instructing caregivers on home treatment.
- 3) For patients with deficits of passive rotation of the neck of > 10 degree or with deficits of passive rotation of the neck of < 10 degrees who have had no improvement after 4 weeks of home treatment, physical therapy is included on this line according to Guideline Note 6 REHABILITATIVE AND HABILITATIVE THERAPIES.

**GUIDELINE NOTE 161, SACROILIAC ANESTHETIC INJECTIONS AND SACROILIAC JOINT FUSION**

*Line 527*

Sacroiliac joint (SIJ) injection (CPT 20610 and 27096, and HCPCS G0260) is included on this line for diagnostic sacroiliac injections with anesthetic only, but not for therapeutic injections or corticosteroid injections. Injections are only covered for patients for whom SIJ fusion surgery is being considered.

SIJ fusion (CPT 27279) is included on this line for patients who have all of the following:

- A) Baseline score of at least 30% on the Oswestry Disability Index (ODI)



**GUIDELINE NOTE 161, SACROILIAC ANESTHETIC INJECTIONS AND SACROILIAC JOINT FUSION (CONT'D)**

- B) Undergone and failed a minimum six months of intensive non-operative treatment that must include non-opioid medication optimization and active therapy. Active therapy is defined as activity modification, chiropractic/osteopathic manipulative therapy, bracing, and/or active therapeutic exercise targeted at the lumbar spine, pelvis, SIJ and hip including a home exercise program. Failure of conservative therapy is defined as less than a 50% improvement on the ODI.
- C) Typically unilateral pain that is caudal to the lumbar spine (L5 vertebrae), localized over the posterior SIJ, and consistent with SIJ pain.
- D) Thorough physical examination demonstrating localized tenderness with palpation over the sacral sulcus (Fortin's point, i.e. at the insertion of the long dorsal ligament inferior to the posterior superior iliac spine or PSIS) in the absence of tenderness of similar severity elsewhere (e.g. greater trochanter, lumbar spine, coccyx) and that other obvious sources for their pain do not exist.
- E) Positive response to at least three of six provocative tests (e.g. thigh thrust test, compression test, Gaenslen's test, distraction test, Patrick's sign, posterior provocation test).
- F) Absence of generalized pain behavior (e.g. somatoform disorder) and generalized pain disorders (e.g. fibromyalgia).
- G) Diagnostic imaging studies that include ALL of the following:
  - 1) Imaging (plain radiographs and a CT or MRI) of the SIJ that excludes the presence of destructive lesions (e.g. tumor, infection), fracture, traumatic sacroiliac joint instability, or inflammatory arthropathy that would not be properly addressed by percutaneous SIJ fusion
  - 2) Imaging of the pelvis (AP plain radiograph) to rule out concomitant hip pathology
  - 3) Imaging of the lumbar spine (CT or MRI) to rule out neural compression or other degenerative condition that can be causing low back or buttock pain
  - 4) Imaging of the SIJ that indicates evidence of injury and/or degeneration
- H) At least 75 percent reduction of pain for the expected duration of two anesthetics (on separate visits each with a different duration of action), and the ability to perform previously painful maneuvers, following an image-guided, contrast-enhanced intra-articular SIJ injection.

**GUIDELINE NOTE 162, LONG-ACTING REVERSIBLE CONTRACEPTIVE (LARC) PLACEMENT**

*Line 6*

Long-acting reversible contraceptives (implant or intrauterine device) are included on Line 6 in all settings, including (but not limited to) immediately postpartum and postabortion.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

**GUIDELINE NOTE 163, SKIN SUBSTITUTES FOR CHRONIC SKIN ULCERS**

*Line 379*

Skin substitutes for chronic venous leg ulcers and chronic diabetic foot ulcers are included on this line when all of the following criteria are met:

- 1) FDA indications and contraindications are followed, if applicable
- 2) Wound has adequate arterial flow (ABI > 0.7), no ongoing infection and a moist wound healing environment
- 3) For patients with diabetes, Hba1c level is < 12
- 4) Prior appropriate wound care therapy (including but not limited to appropriate offloading, multilayer compression dressings and smoking cessation counseling) has failed to result in significant improvement (defined as at least a 50 percent reduction in ulcer surface area) of the wound over at least 30 days
- 5) Ongoing coverage requires significant improvement of the ulcer with skin substitute application over the preceding 6 week time period
- 6) Patients is able to adhere to the treatment plan
- 7) The use of skin substitutes is not included on this line for chronic skin ulcers other than venous leg ulcers and diabetic foot ulcers (e.g., pressure ulcers)

Note: There is no evidence supporting superiority of one skin substitute versus another and new studies are constantly being published. Decisions for specific products could be made based on at least one supportive randomized controlled trial, and those that involve fewer applications, and are lower cost.

**GUIDELINE NOTE 164, PERCUTANEOUS REPAIR OF PARAVALVULAR LEAKS**

*Line 285*

Percutaneous transcatheter closure of paravalvular leak (CPT 93590-93592) is included on this line only for patients with

- 1) prosthetic heart valves with paravalvular leak AND
- 2) intractable hemolysis or NYHA class III/IV heart failure AND
- 3) who are at high risk for surgery and have anatomic features suitable for catheter-based therapy AND
- 4) when performed in centers with expertise in the procedure.



**GUIDELINE NOTE 165, FECAL MICROBIOTA TRANSPLANT**

*Line 146*

Fecal microbiota transplant (FMT); (CPT 44705, HCPCS G0455) is included on this line for treatment of recurrent C difficile infection only.

**GUIDELINE NOTE 166, BREAST REDUCTION SURGERY FOR MACROMASTIA**

*Line 558*

Breast reduction surgery for macromastia is not covered as a treatment for neck or back pain resulting from the macromastia due to lack of high quality evidence of effectiveness.

**GUIDELINE NOTE 167, CHOLECYSTECTOMY FOR CHOLECYSTITIS AND BILIARY COLIC**

*Lines 55,639*

Cholecystectomy for cholecystitis and biliary colic are including on Line 55 when meeting the following criteria:

- A) For cholecystitis, with either:
    - 1) The presence of right upper quadrant abdominal pain, mass, tenderness or a positive Murphy's sign, AND
    - 2) Evidence of inflammation (e.g. fever, elevated white blood cell count, elevated C reactive protein) OR
    - 3) Ultrasound findings characteristic of acute cholecystitis or non-visualization of the gall bladder on oral cholecystogram or HIDA scan, or gallbladder ejection fraction of < 35%.
  - B) For biliary colic (i.e. documented clinical encounter for right upper quadrant or epigastric pain with gallstones seen on imaging during each episode) without evidence of cholecystitis or other complications is included on Line 55 only when
    - 1) Recurrent (i.e. 2 or more episodes in a one year period) OR
    - 2) A single episode in a patient at high risk for complications with emergent cholecystitis (e.g. immunocompromised patients, morbidly obese patients, diabetic patients) OR
    - 3) When any of the following are present: elevated pancreatic enzymes, elevated liver enzymes or dilated common bile duct on ultrasound.
- Otherwise, biliary colic is included on Line 639.

**GUIDELINE NOTE 168, INTRASTROMAL CORNEAL RING SEGMENTS**

*Line 310*

Insertion of intrastromal corneal ring segments (CPT 65785) is included on this line only for reduction or elimination of myopia or astigmatism in adults age 19 and older with keratoconus who are no longer able to achieve adequate functional vision to perform ADLs with best correction using contact lenses or spectacles, who have a corneal thickness of 450 microns or greater at proposed incision site, and for whom corneal transplant is the only remaining option to improve their functional vision.

**GUIDELINE NOTE 169, ORTHODONTICS AND CRANIOFACIAL SURGERY FOR CRANIOFACIAL ANOMALIES**

*Line 257*

Orthodontics and craniofacial surgery are included on this line only for pairing with craniofacial anomaly diagnoses when there is significant malocclusion expected to result in difficulty with mastication, speech, or other oral function. Advanced dental imaging is included on this line only when required for surgical planning for repair of craniofacial anomalies.

**GUIDELINE NOTE 170, INTRATHECAL OR EPIDURAL DRUG INFUSION**

*Lines 71,285,292,489*

Implantation, revision and replacement of devices for intrathecal or epidural drug infusion systems is only included on these lines when the patient meets the criteria for at least one of the categories (A or B) below:

- A) Placed for administration of baclofen for spasticity where all of the following (1-3) occur:
  - 1) The patient has had an adequate trial of non-invasive methods of spasticity control and not had adequate control of spasticity or had intolerable side effects with these methods.
  - 2) The spasticity is causing difficulties with at least one of the following (a, b or c):
    - a) Posture or function
    - b) Balance or locomotion
    - c) Self-care (or ease of care by parents or caregivers)
  - 3) The patient has a favorable response to a trial intrathecal dosage of the anti-spasmodic drug prior to pump implantation.
- B) Palliation for severe, intractable pain due to life-limiting active cancer which
  - 1) Has not been responsive to non-invasive systemic pain control strategies or had intolerable side effects from such strategies, AND
  - 2) Where the patient has a favorable response to a trial of an intrathecal dose of the analgesic drug prior to pump implantation

Intrathecal or epidural drug infusion pump insertion, revision, and replacement are included on Line 660 for use with chronic non-malignant pain and all other indications not listed above. See Guideline Note 173 INTERVENTIONS THAT ARE UNPROVEN, HAVE



**GUIDELINE NOTE 170, INTRATHECAL OR EPIDURAL DRUG INFUSION (CONT'D)**

NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS. Removal of pumps placed for such indications is included on Line 285.

Maintenance (i.e. reprogramming, medication refill) of epidural or intrathecal medication infusion pumps for any condition is only included on these lines for patients who

- A) have no significant complications with the current medication regimen or pump delivery system AND
- B) are continuing to receive adequate benefit from the pump-delivered medication.

Maintenance (but not replacement) of these infusion systems may be paired with ICD-10-CM Z45.49 (Encounter for adjustment and management of other implanted nervous system device).

**GUIDELINE NOTE 171, LATTICE DEGENERATION, ASYMPTOMATIC RETINAL BREAKS AND ROUND HOLES**

*Lines 374,652*

Lattice degeneration is included on Line 374 only for pairing with ophthalmologic visits and dilated eye exams, and only for patients at high risk of retinal detachment:

- A) Patients under the age of 65 years with round holes and myopic vision, OR
- B) Patients with a history of retinal detachment in the other eye OR,
- C) Patients with biologic family member with history of retinal tear or retinal detachment

Otherwise, lattice degeneration is included on Line 652.

Retinal breaks and round holes are only included for pairing with treatment (other than ophthalmologic visits and dilated eye exams) on Line 374 when they are symptomatic, the result of trauma, or are horseshoe breaks. Otherwise, these diagnoses are included on Line 652.

**GUIDELINE NOTE 172, INTERVENTIONS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS**

*Line 500*

The following interventions are prioritized on Line 500 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS:

Procedure Code	Intervention Description	Rationale	Last Review
S2300	Arthroscopy, shoulder, surgical; with thermally-induced capsulorrhaphy	More effective treatments are available	<a href="#">September, 2017</a>
11981 G0516, G0518	Implantable buprenorphine for opioid use disorder for patients who are clinically stable on 8 mg daily or less of buprenorphine or equivalent for at least 6 months	Not cost effective compared to equally efficacious alternative formulations	November, 2017
61630	Balloon angioplasty, intracranial (eg, atherosclerotic stenosis), percutaneous	Similar or worse outcomes than standard therapies	<a href="#">March 2016</a>
64566	Posterior tibial neurostimulation	Minimally effective, no evidence of long-term effectiveness	<a href="#">December, 2010</a>
69710  HCPCS L8690- L8693	Implantation or replacement of electromagnetic bone conduction hearing device in temporal bone  Auditory osseointegrated device	Less effective than other therapies	<a href="#">June, 2014, Aug. 2015</a>
74263, 81528, 81327	Screening CT Colonography, FIT-DNA (Cologuard), mSEPT9, Chromoscopy	Insufficient evidence for use in population screening	<a href="#">September, 2017</a>
94669	Mechanical chest wall oscillation	More costly than equally effective therapies	<a href="#">October, 2016</a>
95250-95251	Retrospective (professional) continuous glucose monitoring	Limited evidence of clinical utility	<a href="#">August, 2017</a>
99174, 99177	Photoscreening	More costly than equally effective methods of screening	<a href="#">November, 2015</a>

**GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS**

*Line 660*

The following Interventions are prioritized on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:



GUIDELINE NOTES FOR THE JANUARY 1, 2018 PRIORITIZED LIST OF HEALTH SERVICES (REVISED)

Procedure Code	Intervention Description	Rationale	Last Review
D0422	Collection and preparation of genetic sample material for laboratory analysis and report	Insufficient evidence of effectiveness	<a href="#">October, 2015</a>
D0423	Genetic test for susceptibility to diseases – specimen analysis		
D9932-D9935	Cleaning and inspection of removable complete or partial denture, maxillary or mandibular	Insufficient evidence of effectiveness	<a href="#">October, 2015</a>
G0106, G0120, G0122	Barium enema as a colorectal cancer screening modality	Not indicated as a CRC screening modality	<a href="#">November, 2017</a>
S9357	Enzyme replacement therapy (e.g. idursulfase and similar medications) for all inborn error of metabolism conditions except infantile Pompe's disease	No clinically important benefit	<a href="#">August, 2012</a>
11981 G0516, G0518	Implantable buprenorphine for opioid use disorder for patients other than those who are clinically stable on 8 mg daily or less of buprenorphine or equivalent for at least 6 months	Unproven treatment	November, 2017
15777	Acellular dermal matrix for soft tissue reinforcement (eg, breast, trunk)	Greater harms than other effective therapies	<a href="#">March, 2015</a>
19294	Intraoperative radiation therapy (IORT) concurrent with partial mastectomy	Unproven treatment	<a href="#">November, 2017</a>
20696-20697	Application of multiplane (pins or wires in more than 1 plane), unilateral, external fixation with stereotactic computer-assisted adjustment (eg, spatial frame)		
20939	Bone marrow aspiration for bone grafting, spine surgery	Unproven treatment	<a href="#">November, 2017</a>
20979	Low intensity ultrasound stimulation to aid bone healing, noninvasive (nonoperative)		
20982	Radiofrequency ablation therapy for reduction or eradication of 1 or more bone tumors	No evidence of effectiveness	2004
20983	Cryotherapy ablation therapy for reduction or eradication of 1 or more bone tumors	No evidence of effectiveness	November, 2014
21685	Hyoid myotomy and suspension		
22867-22870	Insertion of interlaminar/ interspinous process stabilization/ distraction device, without fusion, including image guidance when performed, with open decompression, lumbar	Insufficient evidence of effectiveness	<a href="#">November, 2016</a>
27080	Coccygectomy, primary		
27418	Anterior tibial tubercleplasty (eg, Maquet type procedure)	Harms outweigh benefits, more efficacious procedures exist	May, 2011
28890	Extracorporeal shock wave, high energy involving the plantar fascia		
29866-29867	Arthroscopy, knee, surgical; osteochondral autograft(s)/allograft(s) (eg, mosaicplasty)		
29868	Arthroscopy, knee, surgical; meniscal transplantation		
31627	Computer assisted bronchoscopy	Insufficient evidence of effectiveness	<a href="#">December, 2009</a>
31647-31649, 31651	Bronchial valve insertion/removal/replacement	Insufficient evidence of effectiveness	<a href="#">December, 2012</a>
31660-31661	Bronchial thermoplasty	Insufficient evidence of effectiveness	<a href="#">January, 2014</a>
32998	Radiofrequency ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s)		
33140-33141	Transmyocardial laser revascularization, by thoracotomy		
33340	Percutaneous transcatheter closure of the left atrial appendage with endocardial implant	Insufficient evidence of effectiveness	<a href="#">November, 2016</a>
33548	Surgical ventricular restoration procedure, includes prosthetic patch, when performed (eg, ventricular remodeling, SVR, SAVER, Dor procedures)		



GUIDELINE NOTES FOR THE JANUARY 1, 2018 PRIORITIZED LIST OF HEALTH SERVICES (REVISED)

Procedure Code	Intervention Description	Rationale	Last Review
33927-33929	Total artificial heart	Unproven treatment	<a href="#">November, 2017</a>
36455	Exchange transfusion, blood; other than newborn		
36456	Partial exchange transfusion, blood, plasma or crystalloid necessitating the skill of a physician or other qualified health care professional, newborn	No evidence of effectiveness, evidence of possible harm	<a href="#">November, 2016</a>
36482-36483	Endovenous ablation therapy of incompetent vein, extremity, by transcatheter delivery of a chemical adhesive (eg, cyanoacrylate)	Unproven treatment	<a href="#">November, 2017</a>
41512	Tongue base suspension	No clinically important benefit	<a href="#">January, 2014</a>
41530	Submucosal ablation of the tongue base, radiofrequency		
41821	Operculectomy, excision pericoronal tissue		
43206	Esophagoscopy, flexible, transoral; with optical endomicroscopy	No evidence of effectiveness	December, 2012
43252, 88375	Optical endomicroscopy	Insufficient evidence of effectiveness	<a href="#">December, 2012</a>
43257	Esophagogastroduodenoscopy, flexible, transoral; with delivery of thermal energy to the muscle of lower esophageal sphincter and/or gastric cardia, for treatment of gastroesophageal reflux disease	No evidence of effectiveness	January, 2014
43284	Laparoscopy, surgical, esophageal sphincter augmentation procedure, placement of sphincter augmentation device (ie, magnetic band)	Insufficient evidence of effectiveness	<a href="#">November, 2016</a>
43647-43648 43881-43882	Laparoscopy, surgical; implantation or replacement or revision of gastric neurostimulator electrodes, antrum		
43770, 43842-43845, 43886-43888	Gastric restrictive procedures (gastric band, other)	No evidence of effectiveness	October, 2016
45391-45392	Colonoscopy, flexible; with endoscopic ultrasound examination		
46760-46762	Sphincteroplasty, anal, for incontinence, adult; muscle transplant/implantation artificial sphincter	No evidence of effectiveness	May, 2013
47383	Ablation, 1 or more liver tumor(s), percutaneous, cryoablation	No evidence of effectiveness for both hepatocellular carcinoma and metastatic disease	November, 2013
50380	Renal autotransplantation, reimplantation of kidney		
50592	Radiofrequency ablation, 1 or more renal tumor(s)		
50705	Ureteral embolization or occlusion	Insufficient evidence of effectiveness	<a href="#">November, 2015</a>
52441-52442	Cystourethroscopy, with insertion of permanent adjustable transprostatic implant	No evidence of effectiveness	March, 2015 <a href="#">Coverage Guidance</a>
52647	Laser coagulation of prostate	No evidence of effectiveness	March, 2015 <a href="#">Coverage Guidance</a>
53855	Temporary prostatic stents	Insufficient evidence of effectiveness	<a href="#">October, 2015</a>
53860	Transurethral radiofrequency micro-remodeling of the bladder neck and urethra for stress incontinence	Insufficient evidence of effectiveness	<a href="#">December, 2010</a>
55300	Vasotomy for vasograms, seminal vesiculograms, or epididymogram		
55873	Cryosurgical ablation of the prostate		
55874	Absorbable perirectal spacer for use during prostate cancer radiation therapy	Unproven treatment	<a href="#">November, 2017</a>
58674	Laparoscopy, surgical, ablation of uterine fibroid(s)	Insufficient evidence of effectiveness	<a href="#">November, 2016</a>



GUIDELINE NOTES FOR THE JANUARY 1, 2018 PRIORITIZED LIST OF HEALTH SERVICES (REVISED)

Procedure Code	Intervention Description	Rationale	Last Review
61635	Transcatheter placement of intravascular stent(s), intracranial (eg, atherosclerotic stenosis), including balloon angioplasty, if performed	Results in significantly worse outcomes than medical management	<a href="#">March 2016</a>
61640-61642	Balloon dilation of intracranial vasospasm, percutaneous.	Evidence of harm	<a href="#">March, 2016</a>
61645	Percutaneous arterial transluminal mechanical thrombectomy and/or infusion for thrombolysis, intracranial	No evidence of effectiveness	November, 2015
61650-61651	Endovascular intracranial prolonged administration of pharmacologic agent(s) other than for thrombolysis, arterial	No evidence of effectiveness	November, 2015
62263	Percutaneous lysis of epidural adhesions using solution injection (eg, hypertonic saline, enzyme) or mechanical means		
62290-62292 72285, 72295	Discography		
62380	Endoscopic decompression of spinal cord, nerve root(s), including laminotomy, partial facetectomy, foraminotomy, discectomy and/or excision of herniated intervertebral disc	Insufficient evidence of effectiveness	<a href="#">November, 2016</a>
64479-64480	Transforaminal epidural steroid injections, cervical and thoracic spine	Insufficient evidence of benefit	<a href="#">March, 2015</a>  <a href="#">Coverage Guidance Blog</a>
64490-64492	Facet joint injections cervical and thoracic	Insufficient evidence of benefit	<a href="#">March, 2015</a>  <a href="#">Coverage Guidance Blog</a>
64550, 97014, 97032, 0278T, E0720, E0730, G0283	Transcutaneous electrical nerve stimulation (TENS); Scrambler therapy; Cranial electrical stimulation; all similar transcutaneous electrical neurostimulation therapies	No clinically important benefit (CES) or insufficient evidence of effectiveness (all other) for chronic pain; insufficient evidence of effectiveness for all other indications	<a href="#">September, 2017</a>
64617	Chemodenervation of muscle(s); larynx	No evidence of effectiveness	January, 2014
64633-64634	Radiofrequency ablation of the cervical and thoracic spine	Insufficient evidence of benefit	<a href="#">March, 2015</a>  <a href="#">Coverage Guidance Blog</a>
64635-64636	Radiofrequency ablation of the lumbar and sacral spine	Insufficient evidence of benefit	<a href="#">November, 2014</a>  <a href="#">Coverage Guidance Blog</a>
64912-64913	Nerve repair; with nerve allograft	Unproven treatment	<a href="#">November, 2017</a>
66174-66175	Transluminal dilation of aqueous outflow canal	Insufficient evidence of effectiveness	<a href="#">December, 2010</a>
69720-69725	Decompression facial nerve		
69740-69745	Suture facial nerve		
69955	Total facial nerve decompression and/or repair		
70554-70555	Functional MRI		
74261-74262	Computed tomographic (CT) colonography		
75571	CT coronary calcium scoring	Insufficient evidence of benefit, unclear harms of radiation exposure	<a href="#">August 2013</a>  <a href="#">Coverage Guidance Blog</a>
75572	Computed tomography, heart, with contrast material, for evaluation of cardiac structure and morphology	Insufficient evidence of effectiveness	<a href="#">December, 2009</a>
75574	Computed tomography, heart	Insufficient evidence of benefit, unclear harms of radiation exposure	<a href="#">August, 2013</a>  <a href="#">Coverage Guidance Blog</a>
76376-76377	3D rendering		
77061-77063	Digital breast tomosynthesis	No evidence of effectiveness	November, 2014



GUIDELINE NOTES FOR THE JANUARY 1, 2018 PRIORITIZED LIST OF HEALTH SERVICES (REVISED)

Procedure Code	Intervention Description	Rationale	Last Review
77084	Magnetic resonance (eg, proton) imaging, bone marrow blood supply		
77086	Vertebral fracture assessment using DXA	Insufficient evidence of effectiveness	<a href="#">October, 2015</a>
77767	Remote afterloading high dose rate radionuclide skin surface brachytherapy, includes basic dosimetry	Insufficient evidence of effectiveness	<a href="#">October and November 2015</a>
77768	Skin surface brachytherapy	No evidence of effectiveness	November, 2015
78265-78266	Gastric emptying imaging study	No evidence of effectiveness	November, 2015
78459	Myocardial imaging, positron emission tomography (PET), metabolic evaluation	Insufficient evidence of benefit, unclear harms of radiation exposure	<a href="#">January, 2015</a> <a href="#">Coverage Guidance Blog</a>
78491-78492	Myocardial imaging, positron emission tomography (PET), perfusion	Insufficient evidence of benefit, unclear harms of radiation exposure	<a href="#">January, 2015</a> <a href="#">Coverage Guidance Blog</a>
81225-81227, 81230-81231	Cytochrome P450 gene analysis	Insufficient evidence of effectiveness	December, 2011 <a href="#">November, 2017</a>
81232, 81246	5-fluorouracil/5-FU and capecitabine drug metabolism	Insufficient evidence of effectiveness	<a href="#">November, 2017</a>
81283	IFNL3 (interferon, lambda 3) (eg, drug response), gene analysis, rs12979860 variant	Insufficient evidence of effectiveness	<a href="#">November, 2017</a>
81287	MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis	Insufficient evidence of effectiveness	January, 2014
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) gene analysis, common variants	Insufficient evidence of effectiveness	December, 2011
81328	SLCO1B1 (solute carrier organic anion transporter family, member 1B1) gene analysis, common variant(s)	Insufficient evidence of effectiveness	<a href="#">November, 2017</a>
81330	SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) gene analysis, common variants	Insufficient evidence of effectiveness	December, 2011
81335	TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis	Insufficient evidence of effectiveness	<a href="#">November, 2017</a>
81350	UGT1A1 (UDP glucuronosyl-transferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants	Insufficient evidence of effectiveness	December, 2011
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants	Insufficient evidence of effectiveness	December, 2011
81417	Re-evaluation of whole exome sequencing	Insufficient evidence of effectiveness	December, 2011
81422	Fetal chromosomal microdeletion(s) genomic sequence analysis (eg, DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood	Insufficient evidence of effectiveness	<a href="#">November, 2016</a>
81425-81427	Genome sequence analysis	Insufficient evidence of effectiveness	November, 2014
81470, 81471	X-linked intellectual disability (XLID) genomic sequence panels	Insufficient evidence of effectiveness	November, 2014
81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm	No evidence of effectiveness	November, 2015
81493	Coronary artery disease, mRNA, gene expression profiling	Insufficient evidence of effectiveness	<a href="#">November, 2015</a>
81500	Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing	No evidence of effectiveness	December, 2012



GUIDELINE NOTES FOR THE JANUARY 1, 2018 PRIORITIZED LIST OF HEALTH SERVICES (REVISED)

Procedure Code	Intervention Description	Rationale	Last Review
	serum, with menopausal status, algorithm reported as a risk score		
81503	Oncology (ovarian), biochemical assays of five proteins (CA-125, apolipoprotein A1, beta-2 microglobulin, transferrin, and pre-albumin), utilizing serum, algorithm reported as a risk score	No evidence of effectiveness	December, 2012
81504	Biomarker tests for tumor tissue: <ul style="list-style-type: none"> <li>• Mammaprint, Mammostrat and ImmunoHistoChemistry 4 (IHC4) for breast cancer</li> <li>• Microsatellite instability (MSI) for colorectal cancer</li> <li>• Urovysion for bladder cancer</li> <li>• Prolaris for prostate cancer</li> <li>• Multiple molecular testing to select targeted cancer therapy</li> </ul>	Insufficient evidence of effectiveness. More costly than equally effective therapies for this condition	<a href="#">August, 2015</a> <a href="#">Coverage Guidance Blog</a>
81506	Endocrinology (type 2 diabetes), biochemical assays of seven analytes (glucose, HbA1c, insulin, hs-CRP, adiponectin, ferritin, interleukin 2-receptor alpha), utilizing serum or plasma, algorithm reporting a risk score	No evidence of effectiveness	December, 2012
81521	Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes	Unproven intervention	August, 2015
81535-81536	Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score	No evidence of effectiveness	November, 2015
81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival	No evidence of effectiveness	November, 2015
81539	Oncology (high-grade prostate cancer), biochemical assay of four proteins (Total PSA, Free PSA, Intact PSA, and human kallikrein-2[hk2]), utilizing plasma or serum, prognostic algorithm reported as a probability score	Insufficient evidence of effectiveness	<a href="#">November, 2016</a>
81540	Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported	No evidence of effectiveness	November, 2015
81541	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping)	Unproven intervention	August, 2015
81545	Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result	No evidence of effectiveness	November, 2015
81551	Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1)	Unproven intervention	<a href="#">November, 2017</a>
82107	Alpha-fetoprotein (AFP); AFP-L3 fraction isoform and total AFP		
82610	Cystatin		
82757	Fructose, semen		
82777	Galectin-3	No evidence of effectiveness	November, 2015
83006	Growth stimulation expressed gene 2 (ST2, Interleukin 1 receptor like-1)	No evidence of effectiveness	November, 2014
83037	Hemoglobin; glycosylated (A1C) by device cleared by FDA for home us3		



GUIDELINE NOTES FOR THE JANUARY 1, 2018 PRIORITIZED LIST OF HEALTH SERVICES (REVISED)

Procedure Code	Intervention Description	Rationale	Last Review
83631	Lactoferrin, fecal; quantitative		
83695	Lipoprotein (a)	No evidence of effectiveness	January, 2014
83698	Lipoprotein-associated phospholipase A2 (Lp-PLA2)		
83700-87004	Lipoprotein, blood		
83861	Tear osmolarity		
83951	Oncoprotein; des-gamma-carboxy-prothrombin (DCP)		
83987	pH; exhaled breath condensate	Insufficient evidence of effectiveness	<a href="#">December, 2009</a>
83993	Calprotectin, fecal		
84145	Procalcitonin (PCT)	Insufficient evidence of effectiveness	<a href="#">December, 2009</a>
84431	Thromboxane metabolite(s)	Insufficient evidence of effectiveness	<a href="#">December, 2009</a>
86001	Allergen specific IgG testing	No clinically important benefit	<a href="#">November, 2017</a>
86005	Allergen specific IgE qualitative, multiallergen screen	No clinically important benefit	<a href="#">November, 2017</a>
86006	Allergen specific IgE, multiallergen screen	Harms outweigh benefits	<a href="#">November, 2017</a>
86152-86153	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood)	No evidence of effectiveness	December, 2012
86305	Human epididymis protein 4 (HE4)	Insufficient evidence of effectiveness	<a href="#">December, 2009</a>
86356	Mononuclear cell antigen, quantitative (eg, flow cytometry)		
86386	Nuclear Matrix Protein 22 (NMP22), qualitative	No evidence of effectiveness	December, 2011
87905	Infectious agent enzymatic activity other than virus (eg, sialidase activity in vaginal fluid)		
88738	Hemoglobin (HGB), quantitative, transcutaneous	Insufficient evidence of effectiveness	<a href="#">December, 2009</a>
88740	Hemoglobin, quantitative, transcutaneous, per day; carboxyhemoglobin		
88741	Hemoglobin, quantitative, transcutaneous, per day; methemoglobin		
90845	Psychoanalysis	No longer utilized in clinical practice	
90869	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment	No evidence of effectiveness	December, 2012
90880	Hypnotherapy	No clinically important benefit	<a href="#">August, 2015</a>
91040	Esophageal balloon distension study		
91111	Capsule endoscopy, esophagus	No evidence of effectiveness	December, 2012
91112	Gastrointestinal transit and pressure measurement	Insufficient evidence of effectiveness	<a href="#">December, 2012</a>
91117	Colon motility (manometric) study		
91120	Rectal sensation, tone, and compliance test		
92145	Corneal hysteresis determination	No evidence of effectiveness	November, 2014
92354-92355	Fitting of spectacle mounted low vision aid		
92559	Audiometric testing of groups		
92620-92621	Evaluation of central auditory function		
92625	Assessment of tinnitus		
92640	Diagnostic analysis with programming of auditory brainstem implant		
93050	Arterial pressure waveform analysis for assessment of central arterial pressure	Insufficient evidence of effectiveness	<a href="#">November, 2015</a>
93571-93572	Intravascular Doppler velocity and/or pressure derived coronary flow reserve measurement		
93662	Intracardiac echocardiography during therapeutic/diagnostic intervention		
93702	Bioimpedance spectroscopy (BIS)	No evidence of effectiveness	November, 2014
93740	Temperature gradient studies	Insufficient evidence of effectiveness	<a href="#">October, 2015</a>



Procedure Code	Intervention Description	Rationale	Last Review
93890-93893	Transcranial Doppler study of the intracranial arteries		
93895	Quantitative carotid intima media thickness and carotid atheroma evaluation	No evidence of effectiveness	November, 2014
94452-94453	High altitude simulation test (HAST)		
95012	Nitric oxide expired gas determination		
95803	Actigraphy	No clinically important benefit	<a href="#">January, 2009</a>
95928-95929	Central motor evoked potential study		
96020	Neurofunctional testing selection and administration during noninvasive imaging functional brain mapping		
96116	Neurobehavioral status exam (clinical assessment of thinking, reasoning and judgment, eg, acquired knowledge, attention, language, memory, planning and problem solving, and visual spatial abilities)		
96119	Neuropsychological testing (eg, Halstead-Reitan Neuropsychological Battery, Wechsler Memory Scales and Wisconsin Card Sorting Test)	No evidence of effectiveness	January, 2014
96120	Neuropsychological testing (eg, Wisconsin Card Sorting Test)		
96931-96935	Reflectance confocal microscopy for non-melanoma skin lesions	Insufficient evidence of effectiveness	<a href="#">November, 2015</a>
96936	Reflectance confocal microscopy (RCM) for cellular and subcellular imaging of skin.	Insufficient evidence of effectiveness	<a href="#">November, 2016</a>
97022	Application of a modality; whirlpool	Evidence of harm	<a href="#">May, 2016</a>
97024	Application of a modality; diathermy (eg, microwave)	Insufficient evidence of effectiveness	<a href="#">May, 2016</a>
97028	Application of a modality; ultraviolet	Insufficient evidence of effectiveness	<a href="#">May, 2016</a>
97034	Application of a modality; contrast baths	Insufficient evidence of effectiveness	<a href="#">May, 2016</a>
97035	Application of a modality to 1 or more areas; ultrasound		
97036	Application of a modality; Hubbard tank	Evidence of harm	<a href="#">May, 2016</a>
97533	Sensory integrative techniques to enhance sensory processing and promote adaptive responses to environmental demands		
97610	Low frequency, non-contact, non-thermal ultrasound	No clinically important benefit	<a href="#">October, 2013</a>
<b>HEALTH TECHNOLOGIES CURRENTLY UNDER REVIEW</b>			
81520	Gene expression profiling algorithm for breast cancer mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping),	Under review by HTAS	N/A

**GUIDELINE NOTE 174, CRYOABLATION OF PULMONARY TUMORS***Line 263*

Cryoablation of pulmonary tumors is included on this line only for palliative treatment of an inoperable lung tumor with one of the following:

- A) Symptomatic proximal endobronchial obstruction, OR
- B) Presence of endobronchial lesion with associated lobar or greater parenchymal atelectasis, OR
- C) Hemoptysis from endobronchial location of the tumor.

**GUIDELINE NOTE 175, MEDICATION-ASSISTED TREATMENT OF OPIOID DEPENDENCE†***Lines 1,4*

In patients who meet criteria for opioid use disorder, programs that offer treatment of opioid use disorder must offer patients a variety of evidence-based interventions including behavioral interventions, social support, and Medication Assisted Treatment (MAT) and are individualized to the patient's needs. Intensive programs, such as inpatient residential treatment programs, are required to inform



**GUIDELINE NOTE 175, MEDICATION-ASSISTED TREATMENT OF OPIOID DEPENDENCE† (CONT'D)**

patients about MAT and to offer access to and support for MAT (including at least one form of opioid substitution therapy) if patients elect to receive it, to be included on this line.

MAT includes pharmacotherapy with opioid substitution therapy (methadone and buprenorphine) and opioid antagonists (naltrexone).

Detoxification alone is likely ineffective for producing long-term benefit and should be followed by a formal substance use disorder individualized treatment plan.

In pregnant women with opioid dependence, comprehensive treatment (including opioid substitution therapy) is included on this line.

†Implementation of Guideline Note 175 is being delayed by the Oregon Health Authority until July 1, 2018.

**GUIDELINE NOTE 176, OPPORTUNISTIC SALPINGECTOMY**

*Line 6*

Opportunistic salpingectomy during gynecologic procedures is included on Line 6, when it does not involve an increased payment (i.e., using a form of reference-based pricing) or require a change in the setting in which the procedure would be performed (e.g. necessitate a hospital setting instead of an ambulatory surgical center.)

The development of this guideline note was informed by a HERC [coverage guidance](#). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.



# MULTISECTOR INTERVENTIONS

***Note: The multisector interventions described below are provided as an aid in population health management and do not constitute Oregon Health Plan benefits.***



































*MULTISECTOR INTERVENTIONS  
FOR THE JANUARY 1, 2018 PRIORITIZED LIST OF HEALTH SERVICES (REVISED)*

**MULTISECTOR INTERVENTIONS: TOBACCO PREVENTION AND CESSATION, INCLUDING DURING PREGNANCY**

Benefit coverage for smoking cessation on Line 5 and in Guideline Note 4 TOBACCO DEPENDENCE, INCLUDING DURING PREGNANCY is intended to be offered with minimal barriers, in order to encourage utilization. To further prevent tobacco use and help people quit, additional evidence-based policy and programmatic interventions from a population perspective are available here:

- Oregon Public Health Division's Health Promotion and Chronic Disease Prevention Section: Evidence-Based Strategies for Reducing Tobacco Use A Guide for CCOs  
[http://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/TOBACCO/DOCUMENTS/evidence-based\\_strategies\\_reduce\\_tob\\_use\\_guide\\_cco.pdf](http://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/TOBACCO/DOCUMENTS/evidence-based_strategies_reduce_tob_use_guide_cco.pdf)
- Community Preventive Services Task Force (supported by the CDC) - What Works: Tobacco Use  
<http://www.thecommunityguide.org/about/What-Works-Tobacco-factsheet-and-insert.pdf>

The Community Preventive Services Task Force identified the following evidence-based strategies:

TASK FORCE FINDINGS ON TOBACCO USE	
<p>The Community Preventive Services Task Force (Task Force) has released the following findings on what works in public health to prevent tobacco use. These findings are compiled in The Guide to Community Preventive Services (The Community Guide) and listed in the table below. Use the findings to identify strategies and interventions you could use for your community.</p> <p>Legend for Task Force Findings:  Recommended  Insufficient Evidence  Recommended Against (See reverse for detailed descriptions.)</p>	
Intervention	Task Force Finding
<b>Reducing Tobacco Use Initiation</b>	
Increasing the unit price of tobacco products	
Mass media campaigns when combined with other interventions	
Smoke-free policies	
<b>Increasing Tobacco Use Cessation</b>	
Increasing the unit price of tobacco products	
Mass media campaigns when combined with other interventions	
Mass-reach health communication interventions	
Mobile phone-based interventions	
Multicomponent interventions that include client telephone support	
Smoke-free policies	
Provider reminders when used alone	
Provider reminders with provider education	
Reducing client out-of-pocket costs for cessation therapies	
Internet-based interventions	
Mass media – cessation contests	
Mass media – cessation series	
Provider assessment and feedback	
Provider education when used alone	
Intervention	Task Force Finding
<b>Reducing Exposure to Environmental Tobacco Smoke</b>	
Smoke-free policies	
Community education to reduce exposure in the home	
<b>Restricting Minors' Access to Tobacco Products</b>	
Community mobilization with additional interventions	
Sales laws directed at retailers when used alone	
Active enforcement of sales laws directed at retailers when used alone	
Community education about youth's access to tobacco products when used alone	
Retailer education with reinforcement and information on health consequences when used alone	
Retailer education without reinforcement when used alone	
Laws directed at minors' purchase, possession, or use of tobacco products when used alone	
<b>Decreasing Tobacco Use Among Workers</b>	
Smoke-free policies	
Incentives and competitions to increase smoking cessation combined with additional interventions	
Incentives and competitions to increase smoking cessation when used alone	

Visit the "Tobacco Use" page of The Community Guide website at [www.thecommunityguide.org/tobacco](http://www.thecommunityguide.org/tobacco) to find summaries of Task Force findings and recommendations on tobacco use. Click on each topic area to find results from the systematic reviews, included studies, evidence gaps, and journal publications.

The Centers for Disease Control and Prevention provides administrative, research, and technical support for the Community Preventive Services Task Force.

To reduce the use of tobacco during pregnancy and improve associated outcomes, the evidence supports the following interventions:

- Financial incentives (incentives contingent upon laboratory tests confirming tobacco abstinence are the most effective)
- Smoke-free legislation
- Tobacco excise taxes



*MULTISECTOR INTERVENTIONS  
FOR THE JANUARY 1, 2018 PRIORITIZED LIST OF HEALTH SERVICES (REVISED)*

**MULTISECTOR INTERVENTIONS: PREVENTION OF EARLY CHILDHOOD CARIES**

Evidence supports:

- Community water fluoridation
- Fluoride varnish, including applied in a primary care setting
- Fluoride gel
- Oral fluoride supplementation
- Community-based programs that combine oral health education with supervised toothbrushing

Limited evidence supports:

- Motivational interviewing towards caregivers

Insufficient or conflicting evidence on:

- Anticipatory guidance/oral health education alone
- Encouragement of preventive dental visits
- Risk assessment
- Xylitol products
- Chlorhexidine
- Silver diamine fluoride
- School-based behavioral interventions
- Breastfeeding interventions

**MULTISECTOR INTERVENTIONS: PREVENTION AND TREATMENT OF OBESITY**

Limited evidence supports the following interventions:

- School and childcare settings
- School based interventions to reduce BMI (especially with physical activity focus)
- School nutrition policy and day care meal standards
- Family-based group education programs delivered in schools
- Obesity prevention interventions in childcare settings (nutrition education, healthy cooking classes for 2-6 year olds, physical activity and playful games)

Community level interventions

- Environmental interventions (social marketing, cafeteria signs, farmers markets, walking groups, etc)
- Introduction of light rail
- Community-based group health education and counseling interventions, workplace education interventions
- Workplace and college interventions to improve physical activity

Multiple settings:

- Interventions to reduce sedentary screen time (in some studies, also to increase physical activity and nutrition).
- Multicomponent individual mentored health promotion programs to prevent childhood obesity
- Parental support interventions for diet and physical activity (group education, mental health counseling)

Policy changes

- Sugar sweetened beverage taxes
- Elimination of tax subsidy for advertising unhealthy food to children

This Multisector Interventions statement is based on the work of the HERC Obesity Task Force and the full summary of the evidence report is available at <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.



## MEDICAL POLICY

### Tumor Treatment Field Therapy for Glioblastoma



#### GUIDELINES

**This policy does not certify benefits or authorization of benefits, which is designated by each individual policyholder contract. Paramount applies coding edits to all medical claims through coding logic software to evaluate the accuracy and adherence to accepted national standards. This guideline is solely for explaining correct procedure reporting and does not imply coverage and reimbursement.**

#### DESCRIPTION

Glioblastoma (GBM) is a fast-growing glioma that develops from glial cells in the brain. GBM is the most prevalent and malignant intracranial tumor, representing as much as 30% of primary brain tumors. The overall prognosis is poor, even with the best standard of care. With optimal treatment, the median survival time is approximately 10 to 14 months. Only a third of patients survive for 1 year following diagnosis of GBM, and < 5% live beyond 5 years. Patients with recurrent GBM have a median survival time of just 5 to 7 months.

The incidence of GBM has been shown to increase with age, and is more common in men than women. Exposure to therapeutic or high-dose radiation and rare familial syndromes has been linked to GBM. The current standard of care for newly diagnosed GBM patients is debulking surgery, followed by combination chemotherapy using temozolomide (TMZ) and radiation therapy. Virtually all patients with newly diagnosed GBM relapse despite best available treatment, with a median time to recurrence of approximately 7 months. At the time of disease recurrence, treatment options for GBM patients are limited. Approximately 20% of patients may undergo repeat surgery. Carmustine polymer wafers may be placed intraoperatively in the surgical cavity during repeat surgery. Rarely, patients may undergo reirradiation. For the majority of recurrent GBM patients, chemotherapy is indicated. In the United States, combination treatment with chemotherapy and the angiogenesis inhibitor bevacizumab has been approved for recurrent GBM and certain other cancers. However, approximately 40% to 60% of recurrent GBM patients are either unresponsive to bevacizumab or experience serious adverse events following treatment.

Optune (formerly the NovoTTF-100A System) (Novocure, Portsmouth, NH) is a novel device that emits alternating electric fields, called tumor treatment fields (TTF), that disrupt the rapid cell division exhibited by cancer cells. It has been approved for use in patients with recurrent glioblastoma (GBM) or as a concomitant treatment with temozolomide (TMZ) in patients with newly diagnosed GBM. Its use has also been investigated within clinical trials in patients with cancers other than GBM, including non-small cell lung cancer (NSCLC).

Optune is a portable battery operated device. Treatment parameters are preset by the device manufacturer and no electrical output adjustments are available to patients. The patient must learn to change and recharge depleted device batteries and to connect to an external power supply overnight. Patients carry the device with them to receive continuous treatment, typically recommended for at least 18 hours per day for a minimum of four weeks. Electrodes must be replaced every few days and the scalp reshaved in order to maintain optimal contact.

NovoTAL (Novocure, Portsmouth, NH) is optional software that a physician can purchase and create individualized treatment maps for patients starting Optune. It is performed in-office and uses MRI head morphology, tumor size and location measurements, and tissue di-electric properties to optimize TTF distribution and intensity within the brain tumor. The physicians are required to complete training and certification in order to use the NovoTAL System. The Optune device is available preset from Novocure. The published literature does not indicate that the use of the software for treatment planning with Novotal is superior to using Optune with preset settings or that it improves clinical outcomes.

#### POLICY

**Tumor treatment field (TTF) therapy (i.e., Optune) (E0766) requires prior authorization for all product lines.**

**Treatment planning software (i.e., NovoTAL) for use with TTF therapy is non-covered for all product lines.**

#### HMO, PPO, Individual Marketplace, Elite, Advantage

TTF therapy (i.e., Optune) is considered medically necessary for individuals 22 years of age or older for the following indications:



- Combined TTF and temozolomide in individuals with histologically confirmed newly diagnosed GBM limited to the supratentorial region following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy

OR

- Monotherapy for individuals diagnosed with histologically or radiologically confirmed recurrent GBM limited to the supratentorial region following treatment with chemotherapy after surgical and radiation treatments have been exhausted

TTF therapy is considered investigational and not medically necessary when the criteria above are not met and for all other malignant tumors.

Treatment planning software (i.e., NovoTAL) for use with TTF therapy for any indication is considered experimental, investigational or unproven.

## CODING/BILLING INFORMATION

The appearance of a code in this section does not necessarily indicate coverage. Codes that are covered may have selection criteria that must be met. Payment for supplies may be included in payment for other services rendered.

### HCPCS CODES

<b>A4555</b>	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
<b>E0766</b>	Electrical stimulation device used for cancer treatment, includes all accessories, any type

**TAWG REVIEW DATES:** 05/27/2016, 08/25/2017

## REVISION HISTORY EXPLANATION

**05/27/16:** Policy created to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).

**08/25/17:** Tumor treatment field therapy (E0766) is now covered with prior authorization for all product lines. Treatment planning software (i.e., NovoTAL) for use with TTF therapy for any indication is non-covered for all product lines. Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).

## REFERENCES/RESOURCES

Centers for Medicare and Medicaid Services, CMS Manual System and other CMS publications and services

Ohio Department of Medicaid <http://jfs.ohio.gov/>

American Medical Association, *Current Procedural Terminology (CPT®)* and associated publications and services

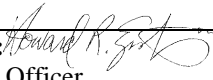
Centers for Medicare and Medicaid Services, Healthcare Common Procedure Coding System, HCPCS Release and Code Sets

Industry Standard Review

Hayes, Inc.



# PreferredOne®

<b>Department of Origin:</b> Integrated Healthcare Services	<b>Approved by:</b>  Chief Medical Officer	<b>Date approved:</b> 01/10/18
<b>Department(s) Affected:</b> Claims, Coding, Customer Service, and Integrated Healthcare Services	<b>Effective Date:</b> 01/24/18	
<b>Medical Policy Document:</b> Durable Medical Equipment, Prosthetics, Orthotics, and Supplies (DMEPOS)	<b>Replaces Effective Policy Dated:</b> 03/03/17	
<b>Reference #:</b> MP/D004	Page 1 of 6	

## PRODUCT APPLICATION:

- ☒ PreferredOne Community Health Plan (PCHP)
- ☒ PreferredOne Administrative Services, Inc. (PAS) ERISA
- ☒ PreferredOne Administrative Services, Inc. (PAS) Non-ERISA
- ☒ PreferredOne Insurance Company (PIC) Individual
- ☒ PreferredOne Insurance Company (PIC) Large Group
- ☒ PreferredOne Insurance Company (PIC) Small Group

**Please refer to the member's benefit document for specific information. To the extent there is any inconsistency between this policy and the terms of the member's benefit plan or certificate of coverage, the terms of the member's benefit plan document will govern.**

**Benefits must be available for health care services. Health care services must be ordered by a physician, physician assistant, or nurse practitioner. Health care services must be medically necessary, applicable conservative treatments must have been tried, and the most cost-effective alternative must be requested for coverage consideration.**

**This policy applies to PAS members only when the employer group has elected to provide benefits for the service/procedure/device. Check benefits in SPD/COC. If benefits not specifically addressed in the SPD/COC verify with the appropriate account manager the availability of benefits.**

## PURPOSE:

To provide coverage guidelines for durable medical equipment (DME), prosthetics, orthotics, and non-durable supplies.

## POLICY:

PCHP/PIC or applicable PAS Plan Administrator will cover medically necessary, physician prescribed equipment, supplies, orthotics, prosthetics, and services a member requires for the therapeutic treatment of an accident or illness subject to the guidelines listed below when eligible under the applicable PCHP/ PIC or Plan Administrator eligible DME, orthotics, prosthetics and supplies (DMEPOS) list. Questions regarding eligibility and/or prior authorization requirements should be directed to the Customer Service department. The appropriate telephone number is listed on the back the member's insurance card.

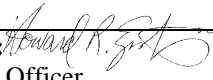
## GUIDELINES:

I. Eligible DME, orthotics, prosthetics, and supplies must satisfy all of the following: A-D

- A. Prior authorized as medically necessary by the Integrated Healthcare Services department when billed charges for purchase exceed \$5000, or as otherwise designated on the DMEPOS List.

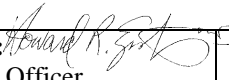
[Note: Unless otherwise designated, rent-to-purchase items do not require prior authorization, even if the purchase price would exceed \$5000.]



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- B. The acceptable standard model that is medically necessary for the member's medical condition. Unacceptable, non-standard models that are not medically necessary include, but are not limited to, the following: 1 and 2
  - 1. DMEPOS that is not proven to be effective by scientific medical literature, and does not demonstrate benefit over standard, less costly equipment; and
  - 2. Any more costly device, which falls under the FDA classification as substantially equivalent to another less costly device.
- C. Ordered for the therapeutic treatment of an accident or illness; to support *activities of daily living*, when required by the COC/SPD. The item is not used primarily for convenience, activities related to leisure, recreation or employment.
- D. Equipment, prosthetics, orthotics, supplies, and services being ordered by a physician is for the treatment of conditions that are allowable by benefits (ie, a chiropractor can only order supplies or equipment used to treat acute musculoskeletal conditions when benefits limit the services of chiropractors to the treatment of acute musculoskeletal conditions)
- E. The frequency is within the allowable quantity limits reflected on the DMEPOS List, unless otherwise specified.
- II. Payment is limited to the most cost effective and medically necessary alternative. When the member purchases a model that is more expensive than what is considered medically necessary the member will be responsible for the difference in purchase and maintenance cost.
- III. Payment for rental shall not exceed the purchase price, unless the item is appropriate for rental only, as designated in this policy. PCHP, PIC, applicable Plan Administrator or designee reserve the right for its medical director or designee to determine if an item will be approved for rental or purchase.
- IV. If a member purchases new equipment or supplies when PCHP, PIC, applicable Plan Administrator or designee determines the repair costs of the member's current equipment or supplies would be more cost effective, then the member will be responsible for the difference in cost.
- V. Payment for repair or replacement of equipment is based on the length of time the equipment has been in service. Payment will not be made for equipment and services when items are damaged or destroyed by the member's misuse, abuse or carelessness; or if they are lost or stolen. Payment will be made only if any of the following apply: A or B
  - A. The equipment is not functioning properly from normal wear and tear and not repairable by the vendor; or
  - B. The physician orders a replacement device or part because of any of the following: 1 or 2
    - 1. A change in the physiological condition of the member; or
    - 2. The condition of the device, or part of the device, requires repairs and the cost of such repairs would be more than 60% of the cost of a replacement device, or of the part being replaced.
- VI. The fact that a provider has prescribed, or recommended an item does not guarantee that the item is medically necessary and/or a covered benefit under the terms of the member's benefit plan.



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VII. All physician-prescribed, medically appropriate and necessary equipment and supplies used in the management and treatment of all forms of diabetes are covered for those plans subject to Minnesota benefit mandates. However, coverage is limited to the most cost-effective acceptable standard equipment.

VIII. Custom-made braces are eligible for coverage only when off-the-shelf items cannot be modified to fit or function properly.

IX. Rental only:

A. PCHP or PIC

1. PCHP or PIC reserves the right for its medical director or designee to determine when an item is appropriate for rental only.
2. PCHP or PIC payment for the following will be considered for rental only reimbursement and not purchase, or rent to purchase; due to frequent and substantial servicing necessary to assure patient safety and positive clinical outcomes.

B. PAS - check SPD for PAS benefits for DME reimbursement, and with appropriate account manager for Plan Administrator position on rental only.

C. The vendor assumes responsibility and liability for duplicates, maintenance, servicing, replacement and supplies necessary for the safety and operation of the item (e.g. breathing circuit, filters, PEEP valve, sterile water, tubing, heated wire circuit, water trap, water chamber etc.).

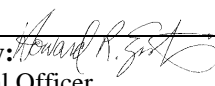
D. Duplicate rental fees for back up ventilators are not eligible, however, rental for a portable in addition to a stationary ventilator may be allowed if medically necessary.

E. Rental only DME may be reviewed periodically for the medical necessity of continued use. The following list is not all-inclusive and current only to the approval date of this policy.

### Rental Only List

DME	HCPCS code
<b>Oxygen and Related Respiratory Equipment</b>	
Stationary compressed gaseous system, includes container, contents, regulator, flowmeter, humidifier, nebulizer, cannula or mask and tubing	E0424
Portable gaseous oxygen system, includes portable container, regulator, flow meter, humidifier, cannula or mask and tubing	E0431
Portable liquid oxygen system, includes portable container, supply reservoir, humidifier, flowmeter, refill adapter, contents gauge, cannula or mask, and tubing	E0434
Stationary liquid oxygen system, includes container, contents, regulator, flowmeter, humidifier, nebulizer, cannula or mask and tubing	E0439
Oxygen concentrator	E1390, E1391, E1392, K0671
Oxygen and water vapor enriching system (with or w/o heated delivery)	E1405, E1406
Oxygen conserving device	No code available



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Respiratory Assist	
Respiratory Assist Device (RAD), bi-level pressure capability, with backup rate feature, used with invasive or noninvasive interface; when being used in place of a ventilator	E0470, E0471, E0472
Respiratory Assist (continued)	
Ventilator (stationary or portable)	E0450, E0460, E0461, E0463, E0464
Miscellaneous	
Bilirubin (phototherapy) light and supplies (blanket cradle)	E0202, E0280
Breast pump (hospital grade)	E0604
Continuous passive motion device (CPM)	E0935, E0936
Electrical stimulation device used for cancer treatment (also known as NovoTTF-100A system [alternating electric field therapy])	E0766, A4555 (transducer)
Negative pressure wound therapy electrical pump, stationary or portable	E2402
Temporary replacement for patient-owned equipment being repaired	K0462

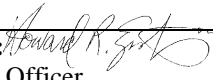
X. Off label use of devices

- A. Off label use of a device that is being investigated as part of a qualifying clinical trial will not be eligible for coverage per guidelines in Medical Policy MP/C008 Oncology Clinical Trials, Covered / Non-Covered Services.
- B. Off label use of devices not in a clinical trial may be approved for one of the following:
  1. Device has unrestricted FDA approval (this does not include Compassionate and Humanitarian FDA approvals)
  2. Published peer reviewed literature supports the therapeutic benefit or diagnostic value

**EXCLUSIONS:**

- I. Refer to the member's Certificate of Coverage or Summary Plan Description for benefits, limitations, and exclusions and the applicable Durable Medical Equipment, Prosthetic, Orthotic, and Supply eligibility list.
- II. Typical plan exclusions include: A-L
  - A. Duplicate or similar items.
  - B. Items which are primarily educational in nature or for vocation, comfort, convenience, or recreation.
  - C. Communication aids or devices; equipment to create, replace or augment communication abilities including, but not limited to, speech processors, receivers, communication board, or computer or electronic assisted communication.



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- D. Household equipment, household fixtures and modifications to the structure of the home, escalators or elevators, ramps, swimming pools, whirlpools, hot tubs and saunas, wiring, plumbing or charges for installation of equipment, exercise cycles, air purifiers, central or unit air conditioners, water purifiers, hypoallergenic pillows, mattresses or waterbeds.
- E. Vehicle/car or van modifications including, but not limited to, hand brakes hydraulic lifts and car carrier.
- F. Over-the-counter orthotics and appliances.
- G. Custom molded foot orthotics.
- H. Orthopedic shoes, except for members with diabetes or peripheral vascular disease.
- I. Items ordered for activities beyond *activities of daily living*, when required by COC/SPD
- J. Charges for sales tax, mailing and delivery.
- K. Items listed as not covered on the DMEPOS List.
- L. Items on the Investigative List.

## DEFINITIONS:

### Activities of Daily Living (ADL):

Physical functions that an independent person performs each day, including bathing, dressing, eating, toileting, walking or wheeling, and transferring into and out of bed. This is equal to a functional ambulation level 1 or 2 for lower limb prosthesis requests. ADLs do not include activities related to leisure, recreation or employment.

### Durable Medical Equipment:

A piece of equipment for a specific therapeutic purpose in the treatment of an illness and that can withstand repeated use and is not disposable; is primarily and customarily used to serve a medical purpose; generally would not be useful to the member in the absence of an illness.

### Healthcare service:

A medical or behavioral pharmaceutical, device, technology, treatment, supply, or procedure

### Non-Durable Equipment/Supplies:

Medical supplies for a specific therapeutic purpose in the treatment of an illness or injury, or are needed for the operation of approved *durable medical equipment* and that are disposable and usually used only one time.

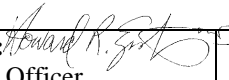
### Orthotic Device:

Rigid or semi-rigid devices used to support a weak or deformed body part or to restrict or eliminate motion in a diseased or injured body part.

### Off Label Use:

Device/equipment/drug used in a manner that is different from its approved purpose



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Prosthetic:

An external device that temporarily or permanently replaces all or part of an external body part, or a device that permanently replaces all or part of the function of an inoperative or malfunctioning internal body part.

**RELATED CRITERIA/POLICIES:**

Integrated Healthcare Services Process Manual: UR015 Use of Medical Policy and Criteria

Medical Policy MP/C008 Clinical Trials

Medical Policy MP/C009 Coverage Determination Guidelines

Medical Policy MP/D008 Dressing Supplies

**REFERENCES:**

1. Minnesota State Statute 62Q.66, 62Q.67, 62A.3093
2. Minnesota Rule: Chapter 4685.0700
3. CMS DME MAC Jurisdiction B DMEPOS/PEN Fee Schedule Code: Frequently Serviced (FS). Retrieved from [https://www.cgsmedicare.com/medicare\\_dynamic/fees/jb/search.asp](https://www.cgsmedicare.com/medicare_dynamic/fees/jb/search.asp).

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## PreferredOne Community Health Plan Nondiscrimination Notice

PreferredOne Community Health Plan ("PCHP") complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. PCHP does not exclude people or treat them differently because of race, color, national origin, age, disability, or sex.

### PCHP:

Provides free aids and services to people with disabilities to communicate effectively with us, such as:

- Qualified sign language interpreters
- Written information in other formats (large print, audio, accessible electronic formats, other formats)

Provides free language services to people whose primary language is not English, such as:

- Qualified interpreters
- Information written in other languages

If you need these services, contact a Grievance Specialist.

If you believe that PCHP has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Grievance Specialist  
PreferredOne Community Health Plan  
PO Box 59052  
Minneapolis, MN 55459-0052  
Phone: 1.800.940.5049 (TTY: 763.847.4013)  
Fax: 763.847.4010  
[customerservice@preferredone.com](mailto:customerservice@preferredone.com)

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, a Grievance Specialist is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at:

U.S. Department of Health and Human Services  
200 Independence Avenue, SW  
Room 509F, HHH Building  
Washington, D.C. 20201  
1-800-368-1019, 800-537-7697 (TDD)

Complaint forms are available at <http://www.hhs.gov/ocr/office/file/index.html>.

## Language Assistance Services

ATTENTION: If you do not speak English, language assistance services, free of charge, are available to you. Call 1.800.940.5049 (TTY: 763.847.4013).

ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 1.800.940.5049 (TTY: 763.847.4013).

LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1.800.940.5049 (TTY: 763.847.4013).

XIYYEEFFANNAA: Afaan dubbattu Oroomiffa, tajaajila gargaarsa afaanii, kanfaltiidhaan ala, ni argama. Bilbilaa 1.800.940.5049 (TTY: 763.847.4013).

CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1.800.940.5049 (TTY: 763.847.4013).

注意：如果您使用繁體中文，您可以免費獲得語言援助服務。請致電 1.800.940.5049 (TTY: 763.847.4013)。

ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода. Звоните 1.800.940.5049 (телетайп: 763.847.4013).

បំពេញ: ប្រសិនបើ អ្នកនិយាយភាសាខ្មែរ, សេវាជំនួយភាសាឥតគិតថ្លៃ គឺអាចមានសំរាប់អ្នក។ ហៅ 1.800.940.5049 (TTY: 763.847.4013)។

ማስታወሻ: የሚናገሩት ቋንቋ አማርኛ ከሆነ የትርጉም አርዳታ ድርጅቶች፡ በነጻ ሊያገኙበት ተዘጋጅተዋል፡ ወደ ሚከተለው ቁጥር ይደውሉ፡ 1.800.940.5049 (ማስማት ለተሳናቸው፡ 763.847.4013)፡፡

ဟံသာဝတီ: နမူနာတို့ ကညီ ကျိအသိ, နမူနာ ကျိအတိအကျတို့ တလက်ကွက်လက်စွာ နှိတ်မိသည့်သွန်လိ။ ကိ: 1.800.940.5049 (TTY: 763.847.4013).

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## MEDICAL POLICY – 1.01.29

## Tumor Treating Fields Therapy for Glioblastoma

Effective Date: Sept. 1, 2016

Last Revised: Mar. 30, 2017

Replaces: N/A

RELATED MEDICAL POLICIES:

None

Select a hyperlink below to be directed to that section.

[POLICY CRITERIA](#) | [CODING](#) | [RELATED INFORMATION](#)[EVIDENCE REVIEW](#) | [REFERENCES](#) | [HISTORY](#)

Clicking this icon returns you to the hyperlinks menu above.

## Introduction

Tumor treating fields (TTF) is a new treatment being studied for use in certain cancers. The therapy consists of low-level electrical currents that arise from small insulated electrodes placed on the skin surface. TTF is believed to cause cell death during a later stage of development. Currently this therapy is covered as one treatment option for people who have a deadly form of brain cancer called glioblastoma multiforme. People wear a helmet with small electrodes attached to the scalp for at least 18 hours per day during TTF therapy. This treatment requires pre-approval by the plan, and this policy describes when this treatment is covered. TTF is considered investigational for other types of cancer (therefore not covered), as there is not yet enough scientific data that shows it works for other diagnoses.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

## Policy Coverage Criteria



Condition	Investigational
<b>Glioblastoma- initial therapy</b>	<b>Tumor treating fields (TTF) to treat glioblastoma is considered investigational:</b> <ul style="list-style-type: none"> <li>As an alternative to standard chemotherapy for patients with advanced or recurrent glioblastoma</li> </ul>
<b>All other diagnoses</b>	<b>Tumor treating fields (TTF) is considered investigational for all other indications.</b>

Condition	Medical Necessity
<b>Glioblastoma- adjuvant therapy</b>	<b>Tumor treating fields (TTF) to treat glioblastoma is medically necessary when all of the following are met:</b> <ul style="list-style-type: none"> <li>Initial treatment with debulking surgery or biopsy, followed by concurrent temozolamide</li> </ul> <b>AND</b> <ul style="list-style-type: none"> <li>Radiotherapy, with no documented tumor progression</li> </ul> <b>AND</b> <ul style="list-style-type: none"> <li>TTF is used with temozolamide</li> </ul> <b>AND</b> <ul style="list-style-type: none"> <li>TTF is begun within 7 weeks of final radiation treatment</li> </ul>

## Coding

HCPCS	
A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
A9900	Miscellaneous DME supply, accessory, and/or service component of another HCPCS code
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type
E1399	Durable medical equipment, miscellaneous

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).





## Related Information

None

## Evidence Review

### Background

#### *Glioblastome Multiforme*

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults. They comprise approximately 15% of all brain and central nervous system tumors, and more than 50% of all tumors that arise from glial cells.<sup>1</sup> The peak incidence for GBM occurs between the ages of 45 and 70 years. GBMs are grade IV astrocytomas, the most deadly type of glial cell tumor, and are often resistant to standard chemotherapy.<sup>1</sup> According to the National Comprehensive Cancer Network, "only a third of patients [with GMB] surviv[e] for 1 year and less than 5% liv[e] beyond 5 years."<sup>2</sup>

#### *Treatment of Glioblastoma Multiforme*

The primary treatment for initial GBM is debulking surgery to remove as much of the tumor as possible. At that time, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea [BCNU]).impregnated wafer.<sup>2</sup> Depending on the patient's physical condition, adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of the 2 are sometimes given. After adjuvant therapy, some patients may undergo maintenance therapy with temozolomide.

No standard treatment exists for recurrent GBM. After these initial treatments, additional debulking surgery may be used if recurrence is localized. Other treatment options for recurrent disease include various forms of systemic medications such as bevacizumab, bevacizumab plus chemotherapy (e.g., irinotecan, BCNU/chloroethylnitrosourea [CCNU], temozolomide), temozolomide, nitrosourea, PCV (procarbazine, CCNU, vincristine), cyclophosphamide, and platinum-based agents.<sup>2</sup> External beam radiotherapy also may be used. Response rates in



recurrent disease are less than 10%, and progression-free survival rates at 6 months are less than 20%.<sup>2,3</sup>

## ***Tumor Treating Fields***

TTF therapy is a new, noninvasive technology intended to treat GBM on an outpatient basis using electrical fields.<sup>3-5</sup> TTF therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis. TTF are proposed to inhibit rapidly dividing tumor cells by two mechanisms: arrest of cell proliferation and destruction of cells while undergoing division.<sup>4,5</sup>

The NovoTTF-100A System has received marketing approval from the U.S. Food and Drug Administration to deliver TTF therapy. TTF therapy via the NovoTTF-100A System is delivered by a battery-powered, portable device that generates the fields via disposable electrodes noninvasively attached to the patient's shaved scalp over the site of the tumor.<sup>3,4</sup> The device is used by the patient at home on a continuous basis (20-24 h/d) for the duration of treatment, which can last for several months. The device is covered under the DME benefit. Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living.<sup>3,4</sup>

## **Evidence Review**

This evidence review was created in August 2013 and has been updated periodically through literature searches of the MEDLINE database. The most recent literature review was through March 24, 2016.

Following is a summary of the key literature. Tumor treating fields (TTF) therapy is proposed as a treatment for glioblastoma multiforme (GBM). For this review, 2 indications will be considered: (1) TTF therapy as an alternative to chemotherapy in advanced or recurrent GBM and (2) TTF therapy as an adjunct to maintenance treatment in patients following early treatment. Comparative trials are essential to determine efficacy in this area, and randomized controlled trials (RCTs) are needed to control for heterogeneity in the patient populations and other confounders of outcome. This evidence review will include both RCTs and nonrandomized comparative trials.





## TTF Therapy as an Alternative to Chemotherapy in Advanced or Recurrent GBM

### *Randomized Controlled Trials*

The U.S. Food and Drug Administration (FDA) approval of the NovoTTF-100A system was based on a Phase III, multinational prospective randomized controlled trial (RCT) (EF11) which was published in 2012 by Stupp et al.<sup>3</sup> The Stupp study, which was sponsored and funded by the manufacturer of the device (NovoCure), compared tumor-treating fields (TTF) therapy (delivered by the NovoTTF-100A System) with the best standard of care chemotherapy (active control). Twenty-eight clinical centers (across 7 countries) enrolled 237 adult participants with relapsed or progressive glioblastoma multiforme (GBM), despite conventional radiotherapy. Other prior treatments may have included surgery and/or chemotherapy. Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky performance status score of 80%. More than 80% of participants had failed 2 or more prior chemotherapy regimens ( $\geq$ second recurrence), and 20% had failed bevacizumab before study enrollment.

Two-hundred thirty-seven patients were randomized in a 1:1 ratio to receive TTF therapy only (n=120) or active control (n=117). The choice of chemotherapy regimens varied, reflecting local practice at each of the participating clinical centers. Chemotherapy agents considered as active control during the trial included platinum-based chemotherapy (i.e., carboplatin); nitrosoureas; procarbazine; combination of procarbazine, lomustine and vincristine (PCV); temozolomide; and bevacizumab. For patients assigned to the TTF group, uninterrupted treatment was recommended, and a period of 28 days of treatment with TTF was considered one full treatment course.

The primary study endpoint in this RCT was overall survival (OS).<sup>3</sup> Secondary endpoints included progression-free survival (PFS) at 6 months, TTP, one-year survival rate, quality of life (QOL), and radiologic response.

Ninety-seven percent (116) of 120 participants in the TTF group started treatment and 93 participants (78%) completed one cycle (4 weeks) of therapy. Discontinuation of TTF therapy occurred in 27 participants (22%) due to noncompliance or the inability to handle the device.<sup>3</sup> For each TTF treatment month, the median compliance was 86% (range, 41%-98%), which equaled a mean use of 20.6 hours per day. In the active control group, 113 (97%) of the 117 assigned participants received chemotherapy and all except one individual completed a full treatment course. Twenty-one participants (18%) in the active control group did not return to the treating site and details on disease progression and toxicity were not available.





Outcomes of this study are summarized in Table 1. The trial failed to reach its primary endpoint of improved survival compared with active chemotherapy. With a median follow-up of 39 months, 220 participants (93%) had died. Median survival was 6.6 months in the TTF group compared with 6.0 months in the active control group (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.66 to 1.12;  $p=0.27$ ). For both groups, one-year survival was 20%.

Longitudinal QOL data were available in 63 participants (27%). There were no meaningful differences observed between the groups in the domains of global health and social functioning. However, cognitive, emotional, and role functioning favored TTF therapy, whereas physical functioning favored chemotherapy. Symptom scale analysis was in accordance to treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.

Wong et al published a subgroup analysis of the Stupp RCT to determine characteristics of responders and nonresponders in the treatment and active control groups.<sup>9</sup> Tumor response was assessed using Macdonald criteria. More patients in the TTF arm were considered responders (14/120 vs 7/117 in the chemotherapy arm.) Median response time was longer for those in the TTF arm (7.3 months) than those in the chemotherapy arm (5.6 months;  $p<0.001$ ), and there was a strong correlation (Pearson  $r$ ) between response and OS in the TTF arm ( $p<0.001$ ) but not in the chemotherapy arm ( $p=0.29$ ). Compared with the chemotherapy arm, a higher proportion of responders in the TTF arm had a prior low-grade histology (36% vs 0%). These differences in treatment responder groups suggest that TTF therapy may differentially benefit certain types of GBM; however, the small numbers of responders in both groups limits generalizations that can be drawn from this analysis.

In summary, this RCT failed to demonstrate the primary endpoint of improved survival with TTF therapy in comparison with chemotherapy.<sup>3,9</sup> Limitations of the trial included a somewhat heterogeneous patient population, with participants included after progression of one or several lines of chemotherapy, as well as the use of different chemotherapy regimens in the control group. Another limitation is the absence of a placebo/supportive care arm. In the setting of advanced disease, the supportive care arm would have been useful to gauge the safety and efficacy of treatment for both groups of patients. Treatments used in the active control arm (best standard of care chemotherapy) in the recurrent disease setting have previously demonstrated limited efficacy, thus limiting the ability to determine the true treatment effect of TTF. Data from a trial of TTF versus placebo, or TTF plus standard chemotherapy versus standard chemotherapy alone would therefore provide a better assessment of treatment efficacy. The latter study design is being used in an ongoing trial of TTF therapy in the treatment of patients with newly diagnosed GBM (see [Ongoing and Unpublished Clinical Trials](#) ).





A further limitation was high dropout rates in both groups. For example, over 20% of participants in the active control group were lost at follow-up, and this degree of the number of dropouts may have underestimated the toxicity evaluation in this group. Similarly, over 20% of participants in the TTF arm discontinued treatment within a few days due to noncompliance or inability to handle the device. This implies that compliance might be an issue with TTF, because it requires the patient to continuously wear transducers on the shaved head. Finally, the number of patients who completed the QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators may have been subject to bias due to the lack of blinding.<sup>3,6</sup>

**Table 1. Principal Efficacy Results for Randomized Trial of TTF Therapy versus Physicians' Choice of Chemotherapy in Recurrent Glioblastoma (Stupp et al)**

Outcomes	TTF	Chemotherapy	Measure of Association, Significance
Median survival, mo	6.6	6.0	
Hazard ratio for survival			0.86 (95% CI, 0.66 to 1.12) favors TTF
Radiologic response (not all patients evaluated)	14%	9.6%	p=0.19
Median PFS, mo	2.2	2.1	
Hazard ratio for PFS			0.81 (95% CI, 0.60 to 1.09) favors TTF

CI: confidence interval; PFS: progression-free survival; TTF: tumor treating fields.

A second post hoc analysis of the TTF EF-11 pivotal trial data was performed to evaluate OS rates among patients who completed at least one complete course of TTF or chemotherapy.<sup>10</sup> These investigators analyzed survival in what they referred to as a "modified ITT [intention-to-treat]" subgroup comprising 93 of 120 (78%) of the original TTF allocated group, versus 117 of 117 (100%) of the original chemotherapy allocated group. This exercise revealed median OS of 7.7 months in the TTF modified ITT (mITT) group compared with 5.9 months in the chemotherapy group (HR=0.69; 95% CI: 0.52 to 0.91; p=0.009). They also showed a trend relationship between proportion of patients with higher TTF compliance and median OS rates (p=0.039). The investigators suggest that TTF provides an OS benefit if used as intended in the





FDA-approved label when compared with best chemotherapy. This post hoc analysis has flaws in that it was not pre-specified in the study, includes only 78% of the original TTF allocated patients, and fails to control for noncompliance due to faster clinical deterioration of TTF recipients leading to treatment cessation.

### ***Nonrandomized Comparative Studies***

Two nonrandomized studies were identified that compared TTF treatment to standard care using historical controls. A study published in late 2014 assessed OS data from 457 patients included in the Patient Registry Dataset (PRiDe), a postmarketing registry of all recurrent GBM patients who received NovoTTF therapy in a real-world, clinical practice setting at 91 centers in the United States between October 2011 and November 2013.<sup>11</sup> Median OS rate in the PRiDe clinical practice dataset (9.6 months) was reported as significantly superior to that attained in the TTF EF-11 pivotal trial (6.6 months; HR=0.66, 95% CI, 0.05 to 0.86;  $p<0.001$ ). One- and 2-year OS rates for TTF in PRiDe were significantly longer than those in the TTF group in the EF-11 trial (44% vs 20% at 1 year; 30% vs 9% at 2 years, respectively). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

Kirson et al (2007) reported findings of a study examining the effects of TTF therapy delivered by the NovoTTF-100A System in 10 patients with recurrent GBM.<sup>12</sup> Median TTP in these patients was 26.1 weeks, and median OS was 62.2 weeks. The authors noted that these TTP and OS rates were more than double the medians reported for historical control patients. No device-related serious adverse events were seen after more than 70 months of cumulative treatment in all patients. The only device-related adverse event observed was a mild-to-moderate contact dermatitis beneath the field delivering electrodes. The primary limitation of this study was its use of historical controls, because those patients may not be comparable on major clinical and prognostic features.<sup>12</sup>

### **Section Summary: TTF Therapy as an Alternative to Chemotherapy in Advanced or Recurrent GBM**

The single RCT for this indication reported that outcomes following TTF therapy were similar to outcomes following standard chemotherapy. However, this RCT is not sufficient to allow conclusions on the efficacy of the device. There was no placebo control group or supportive care treatment group, and treatments used in the active control arm (best standard of care chemotherapy) have previously demonstrated limited efficacy. Thus, the comparisons made have limited ability to determine the true treatment effect of TTF. Methodologic limitations in





the study decrease its' internal validity. There was heterogeneity in the patient populations and heterogeneity in the chemotherapy regimens for the control group. Furthermore, more patients in the TTF group than in the control group did not complete the treatment course, and patients in the TTF group received more courses of second-line chemotherapy. The number of patients who completed the QOL data was approximately one-quarter of total enrollment and the self-reported QOL indicators may have been subject to bias due to the lack of blinding.<sup>3,6</sup> The other available published evidence, 2 nonrandomized comparative studies, are small and limited by potential differences in patient populations. Thus, the evidence base does not permit conclusions about the impact of the technology on health outcomes.

## TTF Therapy as an Adjunct to Standard Maintenance Care for GBM

In 2015, Stupp et al published a planned interim analysis of a multicenter, open-label RCT that evaluated maintenance therapy with TTF for GBM.<sup>13</sup> This trial enrolled patients with GBM who had completed standard treatment consisting of chemoradiotherapy plus surgery if indicated. Patients were randomized in a 2:1 fashion to receive TTF plus temozolomide or temozolomide alone. At the time of the interim analysis, 210 patients were randomized to TTF plus temozolomide and 105 patients randomized to temozolomide alone. The primary outcome was PFS analyzed by intention-to-treat; a secondary outcome was OS analyzed by per-protocol analysis. Planned interim analysis was performed at a median follow-up of 38 months (range, 18-60 months). Median PFS and median OS are summarized in Table 2.

**Table 2. TTF Therapy as an Adjunct to Standard Maintenance Care in Glioblastoma**

Group	N	PFS (95% CI)	HR (98.7% CI)	OS (95% CI)	HR (99.4% CI)
TTF + temozolomide	210 (196a)	7.1 mo (5.9 to 8.2 mo)	0.62 (0.43 to 0.89)	20.5 mo (16.7 to 25 mo)	0.64 (0.42 to 0.98)
Temolozolomide alone	105 (84a)	4.0 mo (3.3 to 5.2 mo)		15.6 mo (13.3 to 19.1 mo)	

CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; TTF: tumor treating fields.<sup>a</sup>  
Included in per-protocol analysis.





There were a total of 35 (11%) dropouts during the trial, 14 (6.7%) of 210 patients in the TTF group and 21 (20%) of 105 in the temozolomide alone group. Adherence to treatment was defined as wearing the device for at least 18 hours a day, and 157 (75%) of 210 patients met this criteria for adherence. The number of treatment cycles with temozolomide differed between groups. The TTF group received a median of 6 cycles compared to a median of 4 cycles for the temozolomide alone group. The most common side effect of treatment was local skin irritation, which occurred in 43% of patients treated with TTF.

### ***Section Summary: TTF Therapy as an Adjunct to Standard Maintenance Care for GBM***

The single RCT for this indication reported that PFS improved by 3.1 months and OS improved by 4.9 months following the addition of TTF to standard maintenance therapy. Therefore, there may be a survival benefit associated with TTF therapy for this indication, but there is substantial uncertainty around this conclusion. The single RCT had methodologic limitations and the current publication is a planned interim analysis. The lack of a placebo group and the lack of blinding create the possibility of a placebo effect, even with the survival outcomes. There was a moderately high rate of dropouts overall (11%) and differential dropout between groups (6.7% in the TTF group vs 20% in standard maintenance group). Also, for outcomes evaluated on a per-protocol basis (e.g., OS), there is the possibility of an adherence bias, in that patients who complete the treatment protocol may have better outcomes than patients who do not. As a result, conclusions about the efficacy of TTF therapy for this indication cannot be made with certainty.

### **Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 3.

**Table 3. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			





<b>NCT01894061<sup>a</sup></b>	A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma	40	October 2016
<b>NCT01755624<sup>a</sup></b>	A Phase II Randomized Study of TTFeld Therapy Versus Supportive Care in Non-small Cell Lung Cancer Patients With 1-5 Brain Metastases Following Optimal Standard Local Treatment	60	July 2017
<b>NCT01756729<sup>a</sup></b>	A Prospective, Non-randomized, Concurrent Control, Open Label, Post-approval Study of NovoTTF-100A in Recurrent GBM Patient	486	January 2018
<b>NCT01954576</b>	A Phase II Study of the NovoTTF-100A system, Enhanced by Genomic Analysis to Identify the Genetic Signature of Response in the Treatment of Recurrent Glioblastoma Multiforme	30	May 2018

NCT: national clinical trial. <sup>a</sup> Denotes industry-sponsored or cosponsored trial.

## Summary of Evidence

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during treatment. Tumor treating fields (TTF).

For individuals who have advanced or recurrent glioblastoma multiforme (GBM) who receive tumor treating fields (TTF) therapy as an alternative to standard chemotherapy, the evidence consists of 1 randomized controlled trial (RCT) and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single published RCT reported no difference in outcomes between patients treated with TTF therapy and standard chemotherapy. This trial has methodologic limitations. The comparisons made included only an active control of questionable efficacy, which may not reflect current standard of care. More patients in the TTF group than in the control group did not complete the treatment course, and patients in the TTF group received more courses of second-line chemotherapy. For the quality of life outcomes, only approximately one-quarter of enrolled patients had complete data. The 2 nonrandomized studies were small, with limited validity due to differences in the patient populations treated with TTF and standard care. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have GBM on maintenance therapy following initial treatment with surgery and/or radiotherapy who receive TTF therapy as an adjunct to maintenance treatment following initial treatment with surgery and/or radiation, the evidence consists of 1 RCT. Relevant





outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT reported that patients who received TTF therapy plus temozolomide have longer progression-free survival (3.1 months) and overall survival (4.9 months) than patients who received temozolomide alone. The trial had methodologic limitations, therefore further high-quality RCTs are needed to validate the results. The evidence is insufficient to determine the effects of the technology on health outcomes.

## Practice Guidelines and Position Statements

The National Comprehensive Cancer Network's Central Nervous System Tumors guidelines (v.1.2016)<sup>2</sup> has updated the recommendation for the treatment of recurrence of glioblastoma, with the option "consider alternating electric field therapy for glioblastomas" from a Category 3 recommendation to a 2A recommendation for adjuvant therapy, and 2B for use in recurrent disease.

## Medicare National Coverage

There is no National Coverage Decision (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

## Regulatory Status

The NovoTTF-100A™ System (assigned the generic name of TTF) was approved by FDA in April 2011 through the premarket approval process.<sup>6</sup> The FDA-approved label reads as follows:

"The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment, and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."<sup>6</sup>

On September 28, 2014, FDA approved a request for Novocure to change its products name from NovoTTF-110A System to Optune™.<sup>7</sup>





On October 15, 2015, FDA granted approval for the use of Optune in combination with temozolomide for newly diagnosed supratentorial glioblastoma, after maximal debulking surgery , radiation and standard chemotherapy<sup>8</sup>

Product code: NZK.

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## History

Date	Comments
10/14/13	New Policy. Policy created with literature search through June 3, 2013; considered investigational.
12/06/13	Update Related Policies. Removed 8.01.31 as it was archived.
11/20/14	Annual Review. Policy updated with literature review through June 26, 2014. References 8 and 16-17 added. Editorial revisions made to rationale section. Policy statement unchanged. New HCPCS codes A9900 and E1399 added to the policy.
10/13/15	Annual Review. Policy updated with literature review through July 8, 2015; references 10-11 removed and 10-12 added. Policy statement unchanged. Removed informational ICD-9 and ICD-10 codes.
08/09/16	Annual Review. Changed statement to MN when criteria are met.
03/30/17	Coding correction; updated code descriptions. Minor formatting update.

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.





## Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:

- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals

PO Box 91102, Seattle, WA 98111

Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357

Email [AppealsDepartmentInquiries@Premera.com](mailto:AppealsDepartmentInquiries@Premera.com)

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at: U.S. Department of Health and Human Services  
 200 Independence Avenue SW, Room 509F, HHH Building  
 Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)  
 Complaint forms are available at  
<http://www.hhs.gov/ocr/office/file/index.html>.

## Getting Help in Other Languages

**This Notice has Important Information.** This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

### አማርኛ (Amharic):

ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ Premera Blue Cross ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀኖች ሊኖሩ ይችላሉ። የጤና ሽፋንዎን ለመጠበቅና በአስፋፈል እርዳታ ለማግኘት በተውሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎታል። ይህን መረጃ እንዲያገኙ እና የለምንም ክፍያ በቋንቋዎ እርዳታ እንዲያገኙ መብት አለዎት።በስልክ ቁጥር 800-722-1471 (TTY: 800-842-5357) ይደውሉ።

### العربية (Arabic):

يحتوي هذا الإشعار معلومات هامة. قد يحوي هذا الإشعار معلومات مهمة بخصوص طلبك أو التغطية التي تريد الحصول عليها من خلال Premera Blue Cross. قد تكون هناك تواريخ مهمة في هذا الإشعار. وقد تحتاج لاتخاذ إجراء في تاريخ معينه للحفاظ على تغطيتك الصحية أو المساعدة في دفع التكاليف. يحق لك الحصول على هذه المعلومات والمساعدة بلغتك دون تكبد أية تكلفة. اتصل بـ 800-722-1471 (TTY: 800-842-5357)

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**本通知有重要的訊息。**本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

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**Cet avis a d'importantes informations.** Cet avis peut avoir d'importantes informations sur votre demande ou la couverture par l'intermédiaire de Premera Blue Cross. Le présent avis peut contenir des dates clés. Vous devrez peut-être prendre des mesures par certains délais pour maintenir votre couverture de santé ou d'aide avec les coûts. Vous avez le droit d'obtenir cette information et de l'aide dans votre langue à aucun coût. Appelez le 800-722-1471 (TTY: 800-842-5357).

### Kreyòl ayisyen (Creole):

**Avi sila a gen enfòmasyon Enpòtan ladann.** Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon yon lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kèk aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resevwa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rele nan 800-722-1471 (TTY: 800-842-5357).

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**Diese Benachrichtigung enthält wichtige Informationen.** Diese Benachrichtigung enthält unter Umständen wichtige Informationen bezüglich Ihres Antrags auf Krankenversicherungsschutz durch Premera Blue Cross. Suchen Sie nach eventuellen wichtigen Terminen in dieser Benachrichtigung. Sie könnten bis zu bestimmten Stichtagen handeln müssen, um Ihren Krankenversicherungsschutz oder Hilfe mit den Kosten zu behalten. Sie haben das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Rufen Sie an unter 800-722-1471 (TTY: 800-842-5357).

### Hmoob (Hmong):

**Tsaw ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb.** Tej zaum tsaw ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj thov kev pab cuam los ntawm Premera Blue Cross. Tej zaum muaj cov hnub tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas peb kom koj ua tsis pub dhau cov caij nyuog uas teev tseg rau hauv daim ntawv no mas koj thiaj yuav tau txais kev pab cuam kho mob los yog kev pab them tej nqi kho mob ntawd. Koj muaj cai kom lawv muab cov ntshiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

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**ភាសាខ្មែរ (Khmer):**

សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរ៉ាប់រងរបស់អ្នកតាមរយៈ Premera Blue Cross ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ចេញសមត្ថភាព ដល់កំណត់ថ្លៃជាក់លាក់នានា ដើម្បីនឹងរក្សាទុកការធានារ៉ាប់រងសុខភាពរបស់អ្នក ឬប្រាក់ជំនួយចេញថ្លៃ។ អ្នកមានសិទ្ធិទទួលព័ត៌មាននេះ និងជំនួយនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-722-1471 (TTY: 800-842-5357)។

**ਪੰਜਾਬੀ (Punjabi):**

ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ Premera Blue Cross ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ . ਇਸ ਨੋਟਿਸ ਜਵਚ ਖਾਸ ਤਾਰੀਖਾਂ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀਂ ਜਸਰਤ ਕਵਰੇਜ ਰਿੱਖਦੀ ਹੋਵੋ ਜਾਂ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਛੁੱਕ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ ਤੋਂ ਪਹਿਲਾਂ ਢੁੱਢ ਖਾਸ ਕਰਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫਤ ਵਿੱਚ ਤੋਂ ਅਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-722-1471 (TTY: 800-842-5357).

**فارسی (Farsi):**

این اعلامیه حاوی اطلاعات مهم میباشد. این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق Premera Blue Cross باشد. به تاریخ های مهم در این اعلامیه توجه نمایید. شما ممکن است برای حفظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کار های خاصی احتیاج داشته باشید. شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-722-1471 (کاربران TTY تماس باشماره 800-842-5357) تماس برقرار نمایید.

**Polskie (Polish):**

To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócić uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-722-1471 (TTY: 800-842-5357).

**Português (Portuguese):**

Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

**Română (Romanian):**

Prezenta notificare conține informații importante. Această notificare poate conține informații importante privind cererea sau acoperirea asigurării dumneavoastră de sănătate prin Premera Blue Cross. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistență privitoare la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-722-1471 (TTY: 800-842-5357).

**Русский (Russian):**

Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

**Fa'asamoa (Samoan):**

Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, Premera Blue Cross, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilo fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'matalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-722-1471 (TTY: 800-842-5357).

**Español (Spanish):**

Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

**Tagalog (Tagalog):**

Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay maaaring naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganiitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

**ไทย (Thai):**

ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับการการสมัครหรือขอเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือในภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 800-722-1471 (TTY: 800-842-5357)

**Український (Ukrainian):**

Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страховального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

**Tiếng Việt (Vietnamese):**

Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình Premera Blue Cross. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-722-1471 (TTY: 800-842-5357).



# ELECTRIC TUMOR TREATMENT FIELD THERAPY

Policy Number: RAD041

Effective Date: January 1, 2019

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## COVERAGE RATIONALE

The use of U.S. Food and Drug Administration (FDA) approved devices to generate electric tumor treatment fields (TTF) to treat newly diagnosed histologically-confirmed Supratentorial glioblastoma (known also as glioblastoma multiforme [GBM] or World Health Organization [WHO] grade IV astrocytoma) is proven and medically necessary when used according to FDA labeled indications, contraindications, warnings and precautions, and when ALL of the following criteria are met:

- Initial treatment with radiation therapy has been completed; and
- Individual is receiving Temozolomide; and
- Individual has a Karnofsky Performance Status (KPS) score of  $\geq 60$ ; and
- Individual or caregiver has been trained and is willing and able to apply the device daily; and
- Individual is willing to wear the device at least 18 hours daily.

### Recurrent GBM

The use of FDA approved devices to generate electric TTF is proven and medically necessary following radiologically-confirmed recurrence of GBM in the supratentorial region of the brain after initial chemotherapy and when ALL of the following criteria are met:

- The device is used as a monotherapy
- Individual has a KPS score of  $\geq 60$ ; and
- Individual or caregiver has been trained and is willing and able to apply the device daily; and
- Individual is willing to wear the device at least 18 hours daily.

When all of the above criteria are met for either newly diagnosed or recurrent GBM, an initial 3 months of electric TTF therapy will be approved.

Subsequent approval(s) for continuation of electric TTF is based on:

- MRI scan has been performed  $\leq 2$ -4 months prior to request and documents no evidence of disease progression. ; and
- KPS score of  $\geq 60$ ; and
- Documentation that the individual has been wearing the device at least 18 hours daily.

The use of devices to generate electric tumor treatment fields (TTF) is considered investigational, unproven, and not medically necessary when the criteria above are not met and for all other indications. The FDA has not approved the use of electric TTF devices for indications other than GBM. Further studies are needed to determine the safety and long-term efficacy of electric TTF therapy for other types of cancer.

Computer software used for therapeutic radiology clinical treatment planning in conjunction with electric tumor treatment field (TTF) therapy is unproven and not medically necessary.

There is insufficient evidence to establish the efficacy of these products in the long-term outcomes of patients receiving electric TTF therapy.

## DEFINITIONS

**Karnofsky Performance Status (KPS):** A standard way of measuring the ability of cancer patients to perform ordinary tasks. KPS scores range from 0 to 100; a higher score means a person is better able to carry out daily



activities. For example, a KPS of 60 means a person requires occasional assistance, but is able to care for most of their personal needs. KPS may be used to determine a patient's prognosis, to measure changes in a patient's ability to function, or to decide if a patient could be included in a clinical trial (National Cancer Institute [NCI], 2018).

**Supratentorial:** The upper portion of the brain comprised of the cerebrum and the diencephalon (NCI, 2018).

**Temozolomide:** An oral alkylating chemotherapy drug used in the treatment of some brain cancers. It is a first-line treatment for glioblastoma (NCI, 2018).

#### APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

CPT Code	Description
77299	Unlisted procedure, therapeutic radiology clinical treatment planning <i>CPT® is a registered trademark of the American Medical Association</i>
HCPCS Code	Description
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type

#### DESCRIPTION OF SERVICES

Electric tumor treatment field (TTF) therapy (also known as tumor-treating fields, TTFields, ETTFs) is based on the principle that low intensity, intermediate frequency electric fields (100 to 300 kHz) have an anti-mitotic effect which acts during late metaphase and anaphase, with specific frequencies affecting specific cell types (Rulseh et al, 2012).

Alternating electrical fields within the human body that disrupt the rapid cell division exhibited by cancer cells, with the alternating electrical fields applied to the brain through transducer arrays placed on the scalp. TTF harness electric fields to arrest the proliferation of tumor cells and to destroy them. The TTF technology takes advantage of the special characteristics and geometrical shape of dividing cells, which make them susceptible to the effects of the alternating electric TTFields. These special fields alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used for a particular treatment is specific to the cell type being treated (e.g., 200kHz for GBM). In contrast, the TTFields have not been shown to have an effect on cells that are not undergoing division. Since most normal adult brain cells proliferate very slowly, if at all, they are hypothesized to be little affected by the TTFields (Novocure, 2018).

Glioblastoma multiforme (GBM) is the most prevalent and primary malignant brain tumor in adults, accounting for 54% of all gliomas. GBM is the most lethal brain tumor with only a third of patients surviving for one year and less than 5% living beyond 5 years. Unfortunately most glioblastomas recur (National Comprehensive Cancer Network [NCCN], 2018). It develops from star-shaped glial cells (astrocytes and oligodendrocytes) that support the health of the nerve cells within the brain.

The mainstay of treatment for GBM is surgery, followed by radiation and chemotherapy. The primary objective of surgery is to remove as much of the tumor as possible without injuring the surrounding healthy brain tissue needed for normal neurological function (such as motor skills, the ability to speak and walk, etc.). However, GBMs are surrounded by a zone of migrating, infiltrating tumor cells that invade surrounding tissues, making it impossible to ever remove the tumor entirely. Surgery provides the ability to reduce the amount of solid tumor tissue within the brain, remove those cells in the center of the tumor that may be resistant to radiation and/or chemotherapy and reduce intracranial pressure (American Association of Neurological Surgeons [AANS], 2018).

The Optune®, formerly the NovoTTF-100A System, (Novocure, Portsmouth NH) was approved by the FDA in April 2011, as a novel device to treat adults age 22 years or older with GBM that recurs or progresses after receiving chemotherapy and radiation therapy.

A supplemental FDA premarket approval was received in October 2015 for Optune™ with Temozolomide in adult patients with newly diagnosed, Supratentorial glioblastoma following maximal debulking surgery and completion of



radiation therapy together with concomitant standard of care chemotherapy. For newly diagnosed GBM, Optune is not intended to be used as a substitute for standard treatments but rather as an adjunct therapy.

Refer to the U.S. Food and Drug Administration (FDA) section for additional information.

The Optune kit contains the portable electric field generator (Optune device), INE (insulated electrode) transducer arrays, power supply, and additional supplies. Prior to treatment, transducer arrays are placed on the patient's scalp according to the tumor's location, which are then covered by a lightweight white cap which resembles a bandage. The patient receives the noninvasive TTF treatment for at least 18 continuous hours per day for a minimum of 4 weeks. As the Optune device is portable, patients are able to carry out every-day activities.

Treatment parameters are preset by the manufacturer such that there are no electrical output adjustments available to the patient. The patient or caregiver must learn to change and recharge depleted device batteries and to connect to an external power supply overnight. In addition, the transducer arrays need to be replaced once to twice a week and the scalp re-shaved in order to maintain optimal contact.

The NovoTAL™ (transducer array layout) system is optional simulation software for use in clinical treatment planning with Optune therapy that may be leased from the manufacturer. Its purpose is to determine the optimal location of the transducer arrays based on the patient's most recent magnetic resonance imaging (MRI) scan, head size, and tumor location.

TTF technology is also being studied through ongoing clinical trials as a treatment for other solid tumors such as non-small cell lung cancer, brain metastasis, pancreatic cancer, ovarian cancer, and mesothelioma.

## CLINICAL EVIDENCE

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline for Central Nervous System Cancers, anaplastic gliomas/glioblastoma, includes standard brain radiation therapy (RT) + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy for patients with good performance status and either methylated or unmethylated/indeterminate MGMT promoter status, in whom resection was not feasible with the following footnote: "Alternating electric field therapy is only an option for patients with supratentorial disease" (category 1). For recurrence of GBM (GLIO-5), the guideline includes consideration of alternating electric treatment fields for glioblastoma after surgery, radiation and chemotherapy (category 2B) (NCCN, 2018).

Stupp et al. (2017) reported final outcomes from the randomized, open-label trial of 695 patients with glioblastoma whose tumor was resected or biopsied and had completed concomitant radiochemotherapy (median time from diagnosis to randomization, 3.8 months) and Optune therapy. Of the 695 randomized patients (median age, 56 years; IQR, 48-63; 473 men [68%]), 637 (92%) completed the trial. Median progression-free survival from randomization was 6.7 months in the TTFields-temozolomide group and 4.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.52-0.76;  $P < .001$ ). Median overall survival was 20.9 months in the TTFields-temozolomide group vs 16.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76;  $P < .001$ ). Systemic adverse event frequency was 48% in the TTFields-temozolomide group and 44% in the temozolomide-alone group. Mild to moderate skin toxicity underneath the transducer arrays occurred in 52% of patients who received TTFields-temozolomide vs no patients who received temozolomide alone. In the final analysis of this randomized clinical trial of patients with glioblastoma who had received standard radiochemotherapy, the addition of TTFields to maintenance temozolomide chemotherapy vs maintenance temozolomide alone, resulted in statistically significant improvement in progression-free survival and overall survival. These results are consistent with the previous interim analysis.

In a secondary analysis of the Stupp et al. (2017) trial, Taphoorn et al. (2018) examined the association of TTFields therapy with progression-free survival and HRQoL among patients with glioblastoma. Of the 695 patients in the study, 639 (91.9%) completed the baseline HRQoL questionnaire. Of these patients, 437 (68.4%) were men; mean (SD) age, 54.8 (11.5) years. Health-related quality of life did not differ significantly between treatment arms except for itchy skin. Deterioration-free survival was significantly longer with TTFields for global health (4.8 vs 3.3 months;  $P < .01$ ); physical (5.1 vs 3.7 months;  $P < .01$ ) and emotional functioning (5.3 vs 3.9 months;  $P < .01$ ); pain (5.6 vs 3.6 months;  $P < .01$ ); and leg weakness (5.6 vs 3.9 months;  $P < .01$ ), likely related to improved progression-free survival. Time to deterioration, reflecting the influence of treatment, did not differ significantly except for itchy skin (TTFields worse; 8.2 vs 14.4 months;  $P < .001$ ) and pain (TTFields improved; 13.4 vs 12.1 months;  $P < .01$ ). Role, social, and physical functioning were not affected by TTFields. The addition of TTFields to standard treatment with temozolomide for patients with glioblastoma results in improved survival without a negative influence on HRQoL except for more itchy skin, an expected consequence from the transducer arrays.

In a multinational, open-label, randomized phase III trial (EF-14 trial), Stupp et al. (2015) compared Optune in combination with temozolomide to temozolomide alone in 700 patients age 18 and over with newly diagnosed GBM.



The interim report revealed that in the intent-to-treat population, patients treated with TTFields plus temozolomide showed a statistically significant increase in progression free survival (PFS), the primary endpoint, compared to temozolomide alone (median PFS 7.1 months versus 4.0 months, hazard ratio=0.62,  $p=0.0013$ ). In the per-protocol population, patients treated with TTFields plus temozolomide demonstrated a statistically significant increase in OS, a powered secondary endpoint, compared to temozolomide alone (median OS 20.5 months versus 15.6 months, hazard ratio=0.64,  $p=0.0042$ ). In the intent-to-treat population, the median OS was 19.6 months versus 16.6 months, respectively, hazard ratio=0.74 ( $p=0.0329$ ). The two-year survival rate was 50 percent greater with TTFields plus temozolomide versus temozolomide alone: 43 percent versus 29 percent. The trial's independent data monitoring committee concluded that the study met its endpoints at its pre-specified interim analysis of the first 315 patients with 18 months or more of follow-up. The committee recommended that the trial be terminated early for success and that all control patients be offered TTFields therapy even prior to progression. In addition, the authors reported that the trial showed Optune could be safely combined with temozolomide. There was no significant increase in systemic toxicities from Optune reported in combination with temozolomide versus temozolomide alone. The most common adverse reaction from Optune treatment was mild to moderate skin irritation, which according to the authors was easily managed, reversible and did not result in treatment discontinuation. This clinical trial has some important limitations. Patient enrollment occurred only after the end of radiochemotherapy, leading to some variation in the delivery of standard treatment of temozolomide and radiotherapy. Patients who had progressed early during radiochemotherapy were not eligible for randomization, thus excluding patients with very poor prognoses. There is likely reporting bias for second-line therapies after tumor progression because in the TTFields plus temozolomide group, TTFields were to be continued, and thus, more detailed treatment information has been tracked for this group.

Stupp et al. (2012) completed a phase III randomized trial (EF-11 trial) of chemotherapy-free treatment of Novo tumor treatment fields (TTF) (20-24h/day) versus active chemotherapy in the treatment of patients with recurrent glioblastoma. The primary end-point was improvement of overall survival. Patients (median age 54 years (range 23-80), Karnofsky performance status 80% (range 50-100) were randomized to TTF alone ( $n=120$ ) or active chemotherapy control ( $n=117$ ). Number of prior treatments was two (range 1-6). Median survival was 6.6 versus 6.0 months (hazard ratio 0.86 [95% CI 0.66-1.12];  $p=0.27$ ), 1-year survival rate was 20% and 20%, progression-free survival rate at 6 months was 21.4% and 15.1% ( $p=0.13$ ), respectively in TTF and active control patients. Responses were more common in the TTF arm (14% versus 9.6%,  $p=0.19$ ). The TTF-related adverse events were mild (14%) to moderate (2%) skin rash beneath the transducer arrays. Severe adverse events occurred in 6% and 16% ( $p=0.022$ ) of patients treated with TTF and chemotherapy, respectively. Quality of life analyses favored TTF therapy in most domains. Although no improvement in overall survival was demonstrated, the authors conclude that the efficacy and activity with this chemotherapy-free treatment device appears comparable to chemotherapy regimens that are commonly used for recurrent glioblastoma and that toxicity and quality of life favored TTF.

A treatment-based analysis of data from the pivotal phase III trial of the NovoTTF-100A System™ versus best physician's choice (BPC) chemotherapy was conducted by Kanner et al. (2014) in patients with recurrent glioblastoma multiforme (GBM), with particular focus on efficacy in patients using NovoTTF therapy as intended. Median overall survival (OS) was compared for recurrent GBM patients receiving at least one full cycle of treatment with NovoTTF-100A System or BPC chemotherapy (modified intention-to-treat [mITT] population). The relationship between NovoTTF-100A System compliance and OS was evaluated in the ITT population. Kaplan-Meier analyses examined treatment-related differences in OS for various patient subgroups. Median OS was significantly higher in patients receiving  $\geq 1$  course of NovoTTF therapy versus BPC (7.7 v 5.9 months; hazard ratio, 0.69; 95% confidence interval [CI], 0.52-0.91;  $P = .0093$ ). Median OS was also significantly higher in patients receiving NovoTTF therapy with a maximal monthly compliance rate  $\geq 75\%$  ( $\geq 18$  hours daily) versus those with a  $< 75\%$  compliance rate (7.7 v 4.5 months;  $P = .042$ ), and Kaplan-Meier analysis demonstrated a significant trend for improved median OS with higher compliance ( $P = .039$ ). Additional post hoc analysis showed significantly higher median OS with NovoTTF therapy than with BPC for patients with prior low-grade glioma, tumor size  $\geq 18$  cm<sup>2</sup>, Karnofsky performance status  $\geq 80$ , and those who had previously failed bevacizumab therapy. This contrasts with the equivalent efficacy reported previously based on analysis of all randomized ITT subjects, including many who did not receive a full cycle of treatment. The authors summarized that results from the present study suggest that when used as intended, NovoTTF Therapy provides efficacy superior to that of chemotherapy in a heterogeneous population of patients with recurrent GBM. Post hoc analyses identified subgroups of patients who may be particularly good candidates for NovoTTF Therapy, pending further confirmatory studies.

Wong et al, (2015) conducted a retrospective chart review from a single institution on patients treated with NovoTTF-100A and bevacizumab between November 2011 and December 2013. The patients were segregated into two cohorts: (i) those treated with NovoTTF-100A and bevacizumab only and (ii) those treated with NovoTTF-100A, bevacizumab and TCCC. Response to treatment was measured according to the Response Assessment in Neuro-Oncology criteria. Progression-free survival (PFS) and OS were measured from the time of application of these treatments to death or last follow up. The cohort treated with NovoTTF-100A, bevacizumab, and TCCC ( $n = 3$ ) did not differ significantly from the rest of the cohort treated with NovoTTF-100A and bevacizumab only ( $n = 34$ ). Potential reasons for this include baseline clinical characteristics and dexamethasone use. The authors note limitations with this review to be the



number of patients treated with NovoTTF-100A, bevacizumab, and TCCC is small and therefore they cannot recommend this combination as standard clinical practice. However, they commented that the findings in their patients are notable and it can serve as a basis for future clinical trials. Second, it is unclear what the relative contribution of immunosuppression in the periphery versus the tumor microenvironment has on treatment resistance in recurrent glioblastomas. Therefore, they conclude that combination treatment, rather than single-agent monotherapy, will more likely affect meaningful clinical results.

Wong et al. (2014) analyzed the characteristics of responders and nonresponders in both cohorts of the phase III trial which compared NovoTTF-100A Best Physician's Choice (BPC) chemotherapy for recurrent glioblastoma to determine the characteristics of response and potential predictive factors. Their analysis showed that a significantly higher proportion of NovoTTF-100A responders, five of 14 (36%), had prior low-grade histologies while none of seven (0%) BPC responder had this type of histological characteristics, suggesting that secondary glioblastoma may be more responsive to NovoTTF-100A treatment. Because primary and secondary glioblastomas have different genetic alterations, notably *EGFR* and *MDM2* amplifications together with *p16* deletion in primary glioblastomas and mutation, *IDH1* mutation and *PDGFR* amplification in secondary glioblastomas, the distinct genetic makeup in these two subtypes of glioblastomas could make secondary glioblastomas more susceptible to NovoTTF-100A treatment. Secondary glioblastomas and low dexamethasone usage are associated with a higher proportion of NovoTTF-100A responders but not BPC chemotherapy responders. The authors surmise that during treatment with NovoTTF-100A, this slower rate of tumor progression might allow enough time for the efficacy of TTF fields to emerge because it may take multiple mitotic cycles to reduce the number of tumor cells and the size of the glioblastoma. The authors recommend that future clinical trials on the NovoTTF-100A device must include stratification of potential predictive factors of response that include both genetic and epigenetic determinants.

Mrugala et al. (2014) evaluated data collected from all adult patients with recurrent GBM who began commercial Novocure TTF therapy through the Patient Registry Dataset (PRiDe), which is a post-marketing registry of all recurrent GBM patients who received NovoTTF therapy in a real-world, clinical practice setting in the United States between 2011 and 2013. Data from 457 recurrent GBM patients who received Novocure TTF therapy in 91 US cancer centers were analyzed. More patients in PRiDe than the EF-11 trial received Novocure TTF therapy for first recurrence (33% v 9%) and had received prior bevacizumab therapy (55.1% v 19%). Median OS was significantly longer with Novocure TTF therapy in clinical practice (PRiDe data set) than in the EF-11 trial (9.6 v 6.6 months; HR, 0.66; 95% CI, 0.05 to 0.86,  $P = .0003$ ). One- and 2-year OS rates were more than double for Novocure TTF therapy patients in PRiDe than in the EF-11 trial (1-year: 44% v 20%; 2-year: 30% v 9%). First and second versus third and subsequent recurrences, high Karnofsky performance status (KPS), and no prior bevacizumab use were favorable prognostic factors. No unexpected adverse events were detected in PRiDe. As in the EF-11 trial, the most frequent adverse events were mild to moderate skin reactions associated with application of the Novocure TTF therapy transducer arrays. The authors concluded that results from PRiDe, together with those previously reported in the EF-11 trial, indicate that Novocure TTF therapy offers clinical benefit to patients with recurrent GBM, has high patient tolerability and favorable safety profile in the real-world, clinical practice setting.

Rulseh et al. (2012) reported the long-term survival of patients with glioblastoma multiforme treated with tumor-treating fields in a small pilot study of 20 individuals. The inclusion criteria of the study included a KPS  $\geq 70\%$  and age  $\geq 18$  years, and the patients were divided into two groups. The first group consisted of 10 patients diagnosed with recurring GBM after failing temozolomide treatment that were treated with TTF field therapy alone, and the second group consisted of 10 newly diagnosed GBM patients at least four weeks post radiation therapy (with adjuvant temozolomide) that received TTF field therapy combined with maintenance temozolomide. The treatment duration in individual patients varied between one and one and a half years, and all histological samples were independently examined in two laboratories in two countries. Twenty percent of the participants in the pilot study (4 out of 20) survived until the time of their report, roughly seven years. The individuals showed no clinical or radiological signs of recurrence and were no longer receiving any treatment. The authors suggest that in order to increase the probability of response to TTF field therapy and subsequent long term survival, TTF field treatment should be continued even in the face of initial radiologic tumor growth.

There is a lack of published evidence from randomized controlled trials examining the long-term safety and effectiveness of TTF as a treatment for tumors other than GBM, including non-small cell lung, brain metastasis, pancreatic cancer, ovarian cancer and mesothelioma.

### **NovoTAL™ Simulation System**

There is limited published clinical evidence related to the NovoTAL™ simulation system, and insufficient data to support improved long-term health outcomes with its use. This includes a small case series (Connelly et al., 2016), human head model (Wenger et al., 2015), and a user group survey (Chaudry et al., 2015). A framework for the use of NovoTAL in treatment planning has been proposed by Trusheim et al. (2016).



## U.S. FOOD AND DRUG ADMINISTRATION (FDA)

The Optune is categorized by the FDA as a stimulator, low electric field, tumor treatment; see the following website for the initial Premarket Approval information: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100034S013>. (Accessed November 09, 2018)

Refer to the following website for additional information on supplemental FDA approvals for the Optune using product code NZK: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm>. (Accessed November 09, 2018)

NovoTAL simulation software is not regulated by the FDA.

## CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for electric tumor treatment field therapy. Local Coverage Determinations (LCDs) exist, see the LCDs for Tumor Treatment Field Therapy (TTFT). (Accessed November 09, 2018)

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#### POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
11/29/2018	Corporate Medical Affairs Committee
11/30/2017	
02/23/2017	

#### INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.



## ***Tumor Treating Fields Therapy for Glioblastoma***

**Effective:** May 1, 2018

**Next Review:** February 201

**Last Review:** March 2018

### **IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

### **DESCRIPTION**

Glioblastoma multiforme is the most common and deadly form of malignant brain tumor in adults. It has a very poor prognosis and is associated with low quality of life during the course of treatment. Tumor treating fields therapy is a new, noninvasive technology that is intended to treat glioblastoma using electrical fields.

### **MEDICAL POLICY CRITERIA**

- I. Tumor treating fields (TTF) to treat primary supratentorial glioblastoma multiforme (GBM) may be considered **medically necessary** when all of the following are met:
  - A. Patient is 18 years of age or older; and
  - B. Documentation of histologically-confirmed primary supratentorial GBM; and
  - C. Following radiation and chemotherapy; and
  - D. Concurrent treatment with temozolomide (TMZ), unless TMZ has been ineffective, not tolerated, or is contraindicated.
- II. The use of mapping software to optimize TTF therapy may be considered **medically necessary** for GBM when patients meet criterion I. above.
- III. The use of TTF and/or TTF-associated mapping software is considered



**investigational** when the above criterion I. is not met.

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

## POLICY GUIDELINES

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Documentation of histologically-confirmed primary supratentorial glioblastoma multiforme (GBM)
- Radiation and chemotherapy history
- Documentation of Temozolomide (TMZ) maintenance treatment and response

## CROSS REFERENCES

None

## BACKGROUND

Glioblastoma multiforme (GBM) are the most common and deadly malignant brain tumor. Glioblastoma is the most common malignant primary brain tumor in adults, with a median age at diagnosis of 64 years.<sup>[1]</sup> GBMs are grade IV astrocytomas, the most deadly type of glial cell tumor, and are often resistant to standard chemotherapy. According to the National Comprehensive Cancer Network (NCCN), GBM is the "deadliest brain tumor with only a third of patients surviving for 1 year and less than 5% living beyond 5 years."<sup>[2]</sup>

The primary treatment for GBM is debulking surgery to remove as much of the tumor as possible. At that time, some patients may undergo implantation of the tumor cavity with a carmustine bis chloroethylnitrosourea (BCNU)-impregnated wafer.<sup>[2]</sup> Depending on the patient's physical condition, adjuvant radiation therapy, chemotherapy (typically temozolomide [TMZ]), or a combination of the two are sometimes given. After adjuvant therapy, some patients may undergo maintenance therapy with TMZ. In patients with disease that recurs after these initial therapies, additional debulking surgery may be used if recurrence is localized. Treatment options for recurrent disease include various forms of systemic medications such as bevacizumab, bevacizumab plus chemotherapy (e.g., irinotecan, BCNU/chloroethylnitrosourea (CCNU), TMZ), TMZ, nitrosourea, PCV (procarbazine, CCNU, and vincristine), cyclophosphamide, and platinum-based agents.<sup>[2]</sup> Response rates in recurrent disease are less than 10%, and progression-free survival rates at 6 months are less than 20%.<sup>[2,3]</sup>

## TUMOR TREATING FIELDS THERAPY

Tumor Treating fields (TTF) therapy is a new, noninvasive technology that is intended to treat GBM on an outpatient basis using electrical fields.<sup>[3-5]</sup> TTF therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis. TTF are proposed to inhibit rapidly dividing tumor cells by 2 mechanisms, arrest of cell proliferation and destruction of cells while undergoing division.<sup>[4,5]</sup>



The Optune™, formerly known as NovoTTF-100A™ System, (Novocure Inc.) has been approved by the U.S. Food and Drug Administration (FDA) to deliver TTF therapy. TTF therapy via the Optune™ is delivered by a battery-powered, portable device that generates the fields via disposable electrodes that are noninvasively attached to the patient's shaved scalp over the site of the tumor.<sup>[3,4]</sup> The device is used by the patient at home on a continuous basis (20-24 hours per day) for the duration of treatment, which can last for several months. Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living.<sup>[3,4]</sup>

## **NOVOTAL™ SYSTEM**

The NovoTAL™ (Transducer Array Layout) System (Novocure Inc.) is a proprietary software tool that produces a custom transducer array layout to optimize Optune therapy for each patient. The software accomplishes this by maximizing the intensity of Tumor Treating Fields (TTFields) based on MRI measurements of the head, tumor size and location(s) and optimizing TTFields distribution.

## **REGULATORY STATUS**

Optune™, (assigned the generic name of TTF) was approved by Food & Drug Administration (FDA) in April 2011 through the premarket approval (PMA) process.<sup>[6]</sup> FDA-approved indication for use are:

“Optune™ is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM).

Optune™ with temozolomide (TMZ), is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy. (FDA PMA approval granted in October 2015)

For the treatment of recurrent GBM, Optune™ is indicated following histologically- or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.”<sup>[7]</sup>

The NovoTAL™ System, was approved by the FDA in November 2013 through a PMA supplement for the Optune™ System. It is the software approved for use by physicians certified to prescribe the Optune™ System.

## **EVIDENCE SUMMARY**

### **PRIMARY GLIOBLASTOMA MULTIFORME**

In 2015, Stupp published interim results of a randomized controlled trial (RCT) regarding the safety and efficacy of TTF used in combination with temozolomide maintenance treatment after chemoradiation therapy for patients with GBM.<sup>[8]</sup> Patients were randomized in a 2:1 fashion to receive maintenance treatment with TTF and TMZ (n=466) or TMZ only (n=229). Study eligibility required patients to be 18 years or older, have a histologically confirmed supratentorial glioblastoma, be progression-free after having undergone maximal safe debulking surgery when feasible or biopsy, and have completed standard concomitant



chemoradiotherapy with TMZ. The median time from diagnosis to randomization was 3.8 months in both groups and patients were not blinded due to ethical concerns. TTF was delivered continuously (> 18 hours/day) via 4 transducers placed on the shaved scalp and TMZ (150-200 mg/m<sup>2</sup>/d) was given for 5 days of each 28-day cycle. Transducer array layouts were determined using the NvoTAL mapping software system for TTF fields to optimize field intensity within the treated tumor. A planned interim analysis was to be conducted on the first 315 patients at 18 months follow-up. The primary study endpoint was progression-free survival (PFS) in the intent-to-treat populations (with a significance threshold of .01) with overall survival (OS) in the per-protocol population (n = 280) as a powered secondary endpoint (significance threshold of .006). A total of 695 patients were enrolled across 83 centers; however the trial was terminated as it met its efficacy endpoints at interim analysis (median 38 months, 315 patients).

The interim analysis included the planned 315 subjects, with 210 in the TTF/TMZ group and 105 in the TMZ only group. The analysis was conducted at a median 38 months follow-up (range, 18-60 months). Prespecified per-protocol median PFS in the TTF/TMZ group was 7.1 months (95% CI, 5.9-8.2 months) compared to 4 months (95% CI, 3.3-5.2 months) in the TMZ only group (hazard ratio [HR], 0.62 [98.7% CI, 0.43-0.89]; P = .001). The median OS in the per-protocol population was statistically improved in the TTF/TMZ group (20.5 months; 95% CI, 16.7-25.0 months) compared to the TMZ only group (15.6 months; 95% CI, 13.3-19.1 months; HR, 0.64 [99.4% CI, 0.42-0.98]; P = .004). An additional analysis of the intention-to-treat population demonstrated and OS of 19.6 months (95% CI, 16.6-24.4 months) in the TTF/TMZ group compared to 16.6 months (95% CI, 13.6-19.2 months) in the TMZ only group (HR, 0.74 [95% CI, 0.56-0.98]; stratified log-rank p = .03). Forty-three percent of patients in the TTF/TMZ group were alive at 2-year follow-up, compared to 29% in the TMZ only group (p = .006).

These interim results demonstrate an approximate three-month improvement of PFS and five-month improvement of OS when TTF therapy is used concurrently with TMZ in patients with newly diagnosed GBM.

In 2017, Stupp published final results from this trial, including all 695 subjects.<sup>[9]</sup> From the time of randomization, median progression-free survival was 6.7 months in the TTF/TMZ group, and 4.0 months in the TMZ only group (HR, 0.63; 95% CI, 0.52-0.76; P < .001). Median overall survival was 20.9 months in the TTF/TMZ group as compared to 16.0 months in the TMZ only group (HR, 0.63; 95% CI, 0.53-0.76; P < .001). The application of TTF therapy in addition to TMZ treatment compared to TMZ treatment alone was not associated with an increase in adverse events (48% vs 44%, P = 0.58). Mild to moderate skin irritation was observed in 52% of patients who received TTF/TMZ treatment.

## **RECURRENT GLIOBLASTOMA MULTIFORME**

The literature on the efficacy of TTF therapy in patients with recurrent GBM consists of small, single-arm studies and two RCTs.

### **Randomized Controlled Trials**

The use of TTF and the corresponding effects on living tissue have been studied in clinical settings.<sup>[10-12]</sup> For example, in 2007, Kirson, reported the findings of a case study examining the effects of TTF therapy delivered by the NovoTTF-100A System in 10 patients with recurrent GBM.<sup>[10]</sup> Median time to progression (TTP) in these patients was 26.1 weeks and



median overall survival (OS) was 62.2 weeks. The authors noted that these TTP and OS values were more than double the reported medians of historical control patients. No device-related serious adverse events were seen after more than 70 months of cumulative treatment in all of the patients. The only device-related adverse event observed was a mild-to-moderate contact dermatitis beneath the field delivering electrodes. The primary limitation of this study was the use of historical controls, since the patients included may not be comparable on major clinical and prognostic features.<sup>[10]</sup>

These preliminary findings served as a basis for a 2012 prospective Phase III multinational RCT by Stupp, which was sponsored and funded by the manufacturer of the device (NovoCure). This study compared TTF therapy (delivered by the NovoTTF-100A System) to the best standard of care chemotherapy (active control).<sup>[3]</sup> Twenty-eight clinical centers (across 7 countries) enrolled 237 adult participants with relapsed or progressive GBM, despite conventional radiotherapy. Other prior treatments may have included surgery and/or chemotherapy. Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky performance status (KPS) of 80%. More than 80% of participants had failed 2 or more prior chemotherapy regimens ( $\geq$  second recurrence), and 20% had failed bevacizumab prior to study enrollment.<sup>[3]</sup>

Two hundred thirty-seven patients were randomized in a 1:1 ratio to receive TTF therapy only (n=120) or active control (n=117). The choice of chemotherapy regimens varied, reflecting local practice at each of the participating clinical centers.<sup>[3]</sup> Chemotherapy agents considered as active control during the trial included platinum-based chemotherapy (i.e., carboplatin); nitrosureas; procarbazine; combination of procarbazine, lomustine and vincristine (PCV); temozolomide; and bevacizumab. For patients assigned to the TTF group, uninterrupted treatment was recommended, although patients were allowed to take treatment breaks of up to 1 hour, twice per day, for personal needs (e.g., shower). In addition, patients assigned to the TTF group were allowed to take 2 to 3 days off treatment at the end of each of 4-week period (which is the minimal required treatment duration for TTF therapy to reverse tumor growth). A period of 28 days of treatment with TTF was considered 1 full treatment course.<sup>[3]</sup>

The primary study end point in this RCT was OS.<sup>[3]</sup> Secondary end points included progression-free survival (PFS) at 6 months, total time to progression (TTP), 1-year survival rate, quality of life (QOL), and radiological response. Participants were seen in clinic monthly, and magnetic resonance imaging (MRI) was performed after 2, 4, and 6 months from initiation of treatment, with subsequent MRIs done according to local practice until disease progression. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with the participants' caregivers were used to assess participant mortality rates.<sup>[3]</sup>

Ninety-seven percent (116) of 120 participants in the TTF group started treatment and 93 participants (78%) completed 1 cycle (4 weeks) of therapy. Discontinuation of TTF therapy occurred in 27 participants (22%) due to noncompliance or the inability to handle the device.<sup>[3]</sup> For each TTF treatment month, the median compliance was 86% (range, 41%-98%), which equaled a mean use of 20.6 hours per day. In the active control group, 113 (97%) of the 117 assigned participants received chemotherapy and all except 1 individual completed a full treatment course. Twenty-one participants (18%) in the active control group did not return to the treating site and details on disease progression and toxicity were not available.<sup>[3]</sup>

This RCT did not reach its primary end point of improved survival compared to active



chemotherapy.<sup>[3]</sup> With a median follow-up of 39 months, 220 participants (93%) had died. Median survival was 6.6 months in the TTF group compared to 6.0 months in the active control group (hazard ratio, 0.86; 95% confidence interval [CI], 0.66 to 1.12;  $p=0.27$ ). For both groups, 1-year survival was 20%. The survival rates for 2- and 3-year survival were 8% and 4%, respectively, for the TTF group versus 5% and 1%, respectively, for the active control group. PFS rate at 6 months was 21.4% in the TTF group, compared to 15.1% in the active control group ( $p=0.13$ ). Objective radiological responses (partial and complete response) were noted in 14 participants in the TTF group and 7 in the active control group, with a calculated response rate of 14.0% (95% CI, 7.9% to 22.4%) compared to 9.6% (95% CI, 3.9% to 18.8%), respectively. Sixteen percent of the TTF participants had grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids. Active control participants experienced grade 2-4 events by organ system related to the pharmacologic activity of chemotherapy agents utilized; severe (grades 3 and 4) toxicity was observed in 3% of participants.<sup>[3]</sup>

Longitudinal QOL data were available in 63 participants (27%).<sup>[3]</sup> There were no meaningful differences observed between the groups in the domains of global health and social functioning. However, cognitive, emotional, and role functioning favored TTF therapy, whereas physical functioning favored chemotherapy. Symptom scale analysis was in accordance to treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the TTF group.

In summary, this RCT failed to demonstrate the primary end point of improved survival with TTF therapy in comparison to chemotherapy.<sup>[3,13]</sup> Limitations of the trial included a somewhat heterogeneous patient population, with participants included after progression of 1 or several lines of chemotherapy, as well as the use of different chemotherapy regimens in the control group. Another limitation is the absence of a placebo/supportive care arm. In the setting of advanced disease, the supportive care arm would have been useful to gauge the safety and efficacy of treatment for both groups of patients. Treatments used in the active control arm (best standard of care chemotherapy) in the recurrent disease setting have previously demonstrated limited efficacy, thus limiting the ability to determine the true treatment effect of TTF. Data from a trial of TTF versus placebo, or of TTF plus standard chemotherapy versus standard chemotherapy alone would therefore provide a better assessment of treatment efficacy.

A further limitation was high dropout rates in both groups. For example, over 20% of participants in the active control group were lost at follow-up, and this may have underestimated the toxicity evaluation in this group. Similarly, over 20% of participants in the TTF arm discontinued treatment within a few days due to noncompliance or inability to handle the device. This implies that compliance might be an issue with TTF, as it requires the patient to continuously wear transducers on the shaved head. Finally, the number of patients who completed the QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators may have been subject to bias due to the lack of blinding.<sup>[3,6]</sup> Therefore, due to the numerous methodologic limitations, evidence from this trial is not sufficient to demonstrate that TTF therapy results in improved health outcomes for patients with recurrent GBM.

Post hoc subgroup analyses of these trial data have been published in abstract form comparing outcomes of patients between both groups who had failed bevacizumab prior to



study enrollment.<sup>[14,15]</sup> For example, Wong et al., published a subgroup analysis of the previously described RCT to determine characteristics of responders and nonresponders in the treatment and active control groups.<sup>[16]</sup> Tumor response was assessed by the Macdonald criteria. More patients in the TTF arm were considered responders (14/120 vs 7/117 in the chemotherapy arm.) Median response time was longer for those in the TTF arm than the chemotherapy arm (7.3 months vs 5.6 months,  $p < 0.001$ ), and there was a strong correlation (Pearson's  $r$ ) between response and OS in the TTF arm ( $p < 0.001$ ) but not in chemotherapy arm ( $p = 0.29$ ). Compared with the chemotherapy arm, a higher proportion of responders in the TTF arm had a prior low-grade histology (36% vs 0%). These differences in treatment responder groups suggest that TTF therapy may differentially benefit certain types of GBM; however, the small numbers of responders in both groups limits generalizations that can be drawn from this analysis.

## **Nonrandomized Studies**

A study published in late 2014 included OS data from 457 patients included in the Patient Registry Dataset (PRiDe), a postmarketing registry of all recurrent GBM patients who received NovoTTF therapy in a real-world, clinical practice setting in 91 centers.<sup>[17]</sup> The median OS rate in the PRiDe clinical practice dataset was reported as significantly superior to that attained in the TTF pivotal trial (9.6 months vs 6.6 months; HR=0.66, 95% CI, 0.05 to 0.86;  $p < 0.001$ ). One- and 2-year OS rates for TTF in PRiDe were significantly longer than those in the TTF group in the pivotal RCT (44% vs 20% at 1 year; 30% vs 9% at 2 years, respectively). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the pivotal RCT. These results, although promising, are limited by a lack of randomized comparison group with which to isolate the direct effect of TTF therapy upon symptom improvement and overall outcomes.

In addition, two very small case series have also been published of long-term survival (>6 years) with TTF therapy.<sup>[18,19]</sup> Since the approval of the NovoTTF device, additional case reports and very small case series ( $n=3-5$ ) have been reported.<sup>[20-22]</sup>

## **NOVOTAL™ SYSTEM**

### **Nonrandomized Studies**

In 2016, Connelly published a small feasibility study using the NovoTAL™ System with nonstandard non-contrast enhancement and advanced imaging.<sup>[23]</sup> All patients presented with gliomas (grades 2-4) and had previously received standard therapy prior to initiation of TTFields. A standard pre- and postcontrast MRI scan was acquired and used for TTFields treatment planning, in conjunction with other imaging modalities. Eight patients were reported on in this series: three underwent T2 imaging, one underwent FLAIR, one used diffusion weighted imaging, and one used MR-perfusion imaging. This case series demonstrates that treatment planning beyond the extent of contrast enhanced MRI is clinically feasible but it must be prospectively compared to standard treatment planning in a clinical trial setting, in order to determine the impact on patient outcomes.

In 2015, Chaudhry et al. evaluated physician performance in conducting transducer array layout mapping using the NovoTAL™ System compared with mapping performed by the Novocure in-house clinical team.<sup>[24]</sup> Fourteen physicians (seven neuro-oncologists, four medical oncologists, and three neurosurgeons) evaluated five blinded cases of recurrent glioblastoma. Concordance for each physician versus Novocure on 20 MRI measurements



was 0.96 (standard deviation, SD  $\pm$  0.03, range 0.90-1.00), indicating very high agreement between the two groups, indicating that physicians prescribing TTFields, when trained on the NovoTAL™ System, can independently perform transducer array layout mapping required for the initiation and maintenance of patients on TTFields therapy. This study did not address clinical utility.

## PRACTICE GUIDELINE SUMMARY

### NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on Central Nervous Systems Tumors (v.1.2017) recommend TTF therapy in conjunction with standard brain radiation therapy and current/adjuvant temozolomide for patients with supratentorial disease with good performance status. This is a category 3 recommendation. The panel conceded that data regarding TTF therapy is limited to evidence from the Stupp RCT which demonstrated similar survival in between groups. In addition, in the background section, the panel indicated that TTF therapy may be considered as a treatment option for recurrent GBM but not all panelists recommend treatment for these patients due to a lack of efficacy. The NCCN guideline does not address the use of TTF therapy recommendation section for patients with recurrent disease.<sup>[2]</sup>

## SUMMARY

The research on the safety and efficacy of tumor treating fields (TTF) therapy for patients with primary glioblastoma has some limitations. However, the small number of studies published do show that TTF therapy improves progression-free and overall survival in adult patients with primary glioblastoma multiforme (GBM) who are receiving concurrent temozolomide (TMZ) treatment. Therefore, TTF therapy may be considered medically necessary when criteria are met. TTF therapy in patients with recurrent glioblastoma multiforme (GBM) is limited to one randomized controlled trial which failed to demonstrate an improvement in overall survival or disease response. Due to insufficient research, the use of TTF therapy is considered investigational when criteria are not met, including but not limited to patients with recurrent glioblastoma.

There is limited research to show that the use of software to optimize tumor treating fields (TTF) therapy (e.g., the NovoTAL™ System) when used in conjunction with TTF therapy improves the outcomes of patients with glioblastoma compared to patients treated with TTF therapy alone. Despite these limitations, the use software to optimize TTF therapy in patients with glioblastoma may be medically necessary when criteria are met. Due to insufficient research, the use of TTF-associated mapping software is considered investigational when criteria are not met.

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## CODES

**NOTE:** There is no specific code for the NovoTAL System software program. While some may submit using CPT code 77261, the appropriate CPT code for this service is unlisted code 77299.

Codes	Number	Description
CPT	77261	Therapeutic radiology treatment planning; simple
	77299	Unlisted procedure, therapeutic radiology clinical treatment planning
HCPCS	A4555	Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only
	E0766	Electrical stimulation device, used for cancer treatment, includes all accessories, any type

**Date of Origin:** January 2014



## Medical Necessity Guidelines: Tumor Treating Fields (TTF)

Effective: December 13, 2017

Clinical Documentation and Prior Authorization Required	✓	Coverage Guideline, No Prior Authorization	
Applies to: <input checked="" type="checkbox"/> Tufts Health Plan Commercial Plans products; Fax: 617.972.9409 <input checked="" type="checkbox"/> Tufts Health Public Plans products <input checked="" type="checkbox"/> Tufts Health Direct – Health Connector; Fax: 888.415.9055 <input checked="" type="checkbox"/> Tufts Health Together – A MassHealth Plan; Fax: 888.415.9055 <input type="checkbox"/> Tufts Health Unify – OneCare Plan; Fax: 781.393.2607 <input checked="" type="checkbox"/> Tufts Health RITogether – A Rhode Island Medicaid Plan; Fax: 857.304.6404 <input checked="" type="checkbox"/> Tufts Health Freedom Plan products; Fax: 617.972.9409			

**Note:** While you may not be the provider responsible for obtaining prior authorization, as a condition of payment you will need to make sure that prior authorization has been obtained.

### OVERVIEW

Glioblastomas (grade IV astrocytomas) are one of the most common types of primary malignant brain tumors in adults. These tumors develop from glial cells in the brain and are usually highly malignant (cancerous) because the cells reproduce quickly and they are supported by a large network of blood vessels. Virtually all patients with newly diagnosed GBM relapse despite best available treatment. At the time of disease recurrence, treatment options for GBM patients are limited. Tumor treating fields (TTF) therapy is administered via a portable medical device that generates low-intensity alternating electric fields, called tumor treating fields. TTF aims to treat recurrent GBM by disrupting the rapid cell division exhibited by malignant cells.

### COVERAGE GUIDELINES

Tufts Health Plan may authorize coverage of TTF therapy as monotherapy in adult patients (22 years of age and older) with histologically-or radiologically-confirmed **recurrent** glioblastoma (GBM) after surgical and radiation options have been exhausted.

### LIMITATIONS

Tufts Health Plan will not cover TTF therapy for the treatment of any condition not outlined above.

### CODES

The following HCPCS code(s) require prior authorization:

**Table 1: HCPCS Codes**

CPT Code	Description
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type
A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only

**Table 3: ICD-10 Codes**

ICD-10 Code	Description
C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles
C71.1	Malignant neoplasm of frontal lobe
C71.2	Malignant neoplasm of temporal lobe
C71.3	Malignant neoplasm of parietal lobe
C71.4	Malignant neoplasm of occipital lobe



ICD-10 Code	Description
C71.5	Malignant neoplasm of cerebral ventricle
C71.6	Malignant neoplasm of cerebellum
C71.7	Malignant neoplasm of brain stem
C71.8	Malignant neoplasm of overlapping sites of brain
C71.9	Malignant neoplasm of brain, unspecified

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## APPROVAL HISTORY

August 10, 2016: Reviewed by the Integrated Medical Policy Advisory Committee (IMPAC), effective January 1, 2017.

Subsequent endorsement date(s) and changes made:

- November 9, 2016: Reviewed by IMPAC, renewed without changes
- February 8, 2017: Reviewed by IMPAC, renewed without changes
- April 2017: Added RITogether Plan product to template. For MNGs applicable to RITogether, effective date is August 1, 2017
- December 13, 2017: Reviewed by IMPAC, renewed without changes

## BACKGROUND, PRODUCT AND DISCLAIMER INFORMATION

Medical Necessity Guidelines are developed to determine coverage for benefits, and are published to provide a better understanding of the basis upon which coverage decisions are made. We make coverage decisions using these guidelines, along with the Member's benefit document, and in coordination with the Member's physician(s) on a case-by-case basis considering the individual Member's health care needs.

Medical Necessity Guidelines are developed for selected therapeutic or diagnostic services found to be safe and proven effective in a limited, defined population of patients or clinical circumstances. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in our service area who are medical experts in the particular field, FDA and other government agency policies, and standards adopted by national accreditation organizations. We revise and update Medical Necessity Guidelines annually, or more frequently if new evidence becomes available that suggests needed revisions.

Medical Necessity Guidelines apply to the fully insured Commercial and Medicaid products when Tufts Health Plan conducts utilization review unless otherwise noted in this guideline or in the Member's benefit document, and may apply to Tufts Health Unify to the same extent as Tufts Health Together. This guideline does not apply to Tufts Medicare Preferred HMO, Tufts Health Plan Senior Care Options or to certain delegated service arrangements. For self-insured plans, coverage may vary depending on the terms of the benefit document. If a discrepancy exists between a Medical Necessity Guideline and a self-insured Member's benefit document, the provisions of the benefit document will govern. Applicable state or federal mandates or other requirements will take precedence. For CareLink<sup>SM</sup> Members, Cigna conducts utilization review so Cigna's medical necessity guidelines, rather than these guidelines, will apply.

Treating providers are solely responsible for the medical advice and treatment of Members. The use of this guideline is not a guarantee of payment or a final prediction of how specific claim(s) will be adjudicated. Claims payment is subject to eligibility and benefits on the date of service, coordination of benefits, referral/authorization, utilization management guidelines when applicable, and adherence to plan policies, plan procedures, and claims editing logic.

[Provider Services](#)



## ELECTRIC TUMOR TREATMENT FIELD THERAPY

**Policy Number:** CS146.B

**Effective Date:** November 1, 2017

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### Related Community Plan Policy

- [Clinical Trials](#)

### Commercial Policy

- [Electric Tumor Treatment Field Therapy](#)

### INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced. The terms of the federal, state or contractual requirements for benefit plan coverage may differ greatly from the standard benefit plan upon which this Medical Policy is based. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage supersede this Medical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the contractual requirements for benefit plan coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

### BENEFIT CONSIDERATIONS

Before using this policy, please check the federal, state or contractual requirements for benefit coverage.

### COVERAGE RATIONALE

**The use of U.S. Food and Drug Administration (FDA) approved devices to generate electric tumor treatment fields (TTF) to treat histologically-confirmed Supratentorial glioblastoma (known also as glioblastoma multiforme [GBM] or World Health Organization [WHO] grade IV astrocytoma) is proven and medically necessary as adjunctive therapy when used according to FDA labeled indications, contraindications, warnings and precautions, and when ALL of the following criteria are met:**

- Initial treatment with debulking surgery or biopsy followed by chemoradiation with concomitant Temozolomide and radiotherapy has been completed; and
- Individual has Karnofsky Performance Status (KPS) score of >60; and
- Individual or caregiver has been trained and is willing and able to apply the device daily; and
- Individual is willing to wear the device at least 18 hours daily.

When all of the above criteria are met, an initial 3 months of electric TTF therapy will be approved.

Subsequent approval(s) for continuation of electric TTF is based on:

- Evidence of no documented disease progression by magnetic resonance imaging (MRI) done at a minimum of every 2-4 months. This includes a completed MRI scan with report submitted as part of any request for continuation of electric TTF treatment; and



- KPS score of >60; and
- Documentation that the individual and/or caregiver have been applying the device daily; and
- Documentation that the patient has been wearing the device at least 18 hours daily.

**The use of devices to generate electric tumor treatment fields (TTF) is considered investigational, unproven, and not medically necessary when the criteria above are not met and for all other indications.** The FDA has not approved the use of electric TTF devices for indications other than GBM. Further studies are needed to determine the safety and long-term efficacy of electric TTF therapy for other types of cancer.

**Computer software used for therapeutic radiology clinical treatment planning in conjunction with electric tumor treatment field (TTF) therapy is unproven and not medically necessary.** There is insufficient evidence to establish the efficacy of these products in the long-term outcomes of patients receiving electric TTF therapy.

## DEFINITIONS

Please check the definitions within the member benefit plan document that supersede the definitions below.

**Karnofsky Performance Status (KPS):** A standard way of measuring the ability of cancer patients to perform ordinary tasks. KPS scores range from 0 to 100; a higher score means a person is better able to carry out daily activities. For example, a KPS of 60 means a person requires occasional assistance, but is able to care for most of their personal needs. KPS may be used to determine a patient's prognosis, to measure changes in a patient's ability to function, or to decide if a patient could be included in a clinical trial.

**Supratentorial:** The upper portion of the brain comprised of the cerebrum and the diencephalon.

**Temozolomide:** An oral alkylating chemotherapy drug used in the treatment of some brain cancers. It is a first-line treatment for glioblastoma.

## APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

CPT Code	Description
77299	Unlisted procedure, therapeutic radiology clinical treatment planning <i>CPT® is a registered trademark of the American Medical Association</i>
HCPCS Code	Description
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type

## DESCRIPTION OF SERVICES

Electric tumor treatment field (TTF) therapy (also known as tumor-treating fields, TTFields, ETTFs) is based on the principle that low intensity, intermediate frequency electric fields (100 to 300 kHz) have an anti-mitotic effect which acts during late metaphase and anaphase, with specific frequencies affecting specific cell types (Rulseh et al, 2012).

Alternating electrical fields within the human body that disrupt the rapid cell division exhibited by cancer cells, with the alternating electrical fields applied to the brain through transducer arrays placed on the scalp. TTF harness electric fields to arrest the proliferation of tumor cells and to destroy them. The TTF technology takes advantage of the special characteristics and geometrical shape of dividing cells, which make them susceptible to the effects of the alternating electric TTFields. These special fields alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used for a particular treatment is specific to the cell type being treated (e.g., 200kHz for GBM). In contrast, the TTFields have not been shown to have an effect on cells that are not undergoing division. Since most normal adult brain cells proliferate very slowly, if at all, they are hypothesized to be little affected by the TTFields. (Novocure, 2017)



Glioblastoma multiforme (GBM) is the most prevalent and primary malignant brain tumor in adults, accounting for 54% of all gliomas. GBM is the most lethal brain tumor with only a third of patients surviving for one year and less than 5% living beyond 5 years. Unfortunately most glioblastomas recur (NCCN, 2016). It develops from star-shaped glial cells (astrocytes and oligodendrocytes) that support the health of the nerve cells within the brain.

The mainstay of treatment for GBM is surgery, followed by radiation and chemotherapy. The primary objective of surgery is to remove as much of the tumor as possible without injuring the surrounding healthy brain tissue needed for normal neurological function (such as motor skills, the ability to speak and walk, etc.). However, GBMs are surrounded by a zone of migrating, infiltrating tumor cells that invade surrounding tissues, making it impossible to ever remove the tumor entirely. Surgery provides the ability to reduce the amount of solid tumor tissue within the brain, remove those cells in the center of the tumor that may be resistant to radiation and/or chemotherapy and reduce intracranial pressure. [American Association of Neurological Surgeons (AANS), 2015]

The Optune<sup>®</sup>, formerly the NovoTTF-100A System, (Novocure, Portsmouth NH) was approved by the FDA in April 2011, as a novel device to treat adults age 22 years or older with GBM that recurs or progresses after receiving chemotherapy and radiation therapy.

A supplemental FDA premarket approval was received in October 2015 for Optune<sup>™</sup> with Temozolomide in adult patients with newly diagnosed, Supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy. For newly diagnosed GBM, Optune is not intended to be used as a substitute for standard treatments but rather as an adjunct therapy.

Refer to the [U.S. Food and Drug Administration \(FDA\)](#) section for additional information.

The Optune kit contains the portable electric field generator (Optune device), INE (insulated electrode) transducer arrays, power supply, and additional supplies. Prior to treatment, transducer arrays are placed on the patient's scalp according to the tumor's location, which are then covered by a lightweight white cap which resembles a bandage. The patient receives the noninvasive TTF treatment for at least 18 continuous hours per day for a minimum of 4 weeks. As the Optune device is portable, patients are able to carry out every-day activities.

Treatment parameters are preset by the manufacturer such that there are no electrical output adjustments available to the patient. The patient or caregiver must learn to change and recharge depleted device batteries and to connect to an external power supply overnight. In addition, the transducer arrays need to be replaced once to twice a week and the scalp re-shaved in order to maintain optimal contact.

The NovoTAL<sup>™</sup> (transducer array layout) system is optional simulation software for use in clinical treatment planning with Optune therapy that may be leased from the manufacturer. Its purpose is to determine the optimal location of the transducer arrays based on the patient's most recent magnetic resonance imaging (MRI) scan, head size, and tumor location.

TTF technology is also being studied through ongoing clinical trials as a treatment for other solid tumors such as non-small cell lung cancer, brain metastasis, pancreatic cancer, ovarian cancer and mesothelioma.

## CLINICAL EVIDENCE

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline for Central Nervous System Cancers, anaplastic gliomas/glioblastoma GLIO-3 and GLIO-4, includes standard brain radiation therapy (RT) + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy for patients with good performance status and either methylated or unmethylated/indeterminate MGMT promoter status, with the following footnote: "Alternating electric field therapy is only an option for patients with supratentorial disease" (category 2A). For recurrence of GBM (GLIO-5), the guideline includes consideration of alternating electric treatment fields for glioblastoma after surgery, radiation and chemotherapy (category 2B) (NCCN, 2016).

In a multinational, open-label, randomized phase III trial (EF-14 trial), Stupp et al. (2015) compared Optune in combination with temozolomide to temozolomide alone in 700 patients age 18 and over with newly diagnosed GBM. The interim report revealed that in the intent-to-treat population, patients treated with TTFields plus temozolomide showed a statistically significant increase in progression free survival (PFS), the primary endpoint, compared to temozolomide alone (median PFS 7.1 months versus 4.0 months, hazard ratio=0.62, p=0.0013). In the per-protocol population, patients treated with TTFields plus temozolomide demonstrated a statistically significant increase in OS, a powered secondary endpoint, compared to temozolomide alone (median OS 20.5 months versus 15.6 months, hazard ratio=0.64, p=0.0042). In the intent-to-treat population, the median OS was 19.6 months versus 16.6 months, respectively, hazard ratio=0.74 (p=0.0329). The two-year survival rate was 50 percent greater with TTFields plus temozolomide versus temozolomide alone: 43 percent versus 29 percent. The trial's independent data monitoring



committee concluded that the study met its endpoints at its pre-specified interim analysis of the first 315 patients with 18 months or more of follow-up. The committee recommended that the trial be terminated early for success and that all control patients be offered TTFields therapy even prior to progression. In addition, the authors reported that the trial showed Optune could be safely combined with temozolomide. There was no significant increase in systemic toxicities from Optune reported in combination with temozolomide versus temozolomide alone. The most common adverse reaction from Optune treatment was mild to moderate skin irritation, which according to the authors was easily managed, reversible and did not result in treatment discontinuation. This clinical trial has some important limitations. Patient enrollment occurred only after the end of radiochemotherapy, leading to some variation in the delivery of standard treatment of temozolomide and radiotherapy. Patients who had progressed early during radiochemotherapy were not eligible for randomization, thus excluding patients with very poor prognoses. There is likely reporting bias for second-line therapies after tumor progression because in the TTFields plus temozolomide group, TTFields were to be continued, and thus, more detailed treatment information has been tracked for this group.

Stupp et al. (2012) completed a phase III randomized trial (EF-11 trial) of chemotherapy-free treatment of Novo tumor treatment fields (TTF) (20-24h/day) versus active chemotherapy in the treatment of patients with recurrent glioblastoma. The primary end-point was improvement of overall survival. Patients (median age 54 years (range 23-80), Karnofsky performance status 80% (range 50-100) were randomized to TTF alone (n=120) or active chemotherapy control (n=117). Number of prior treatments was two (range 1-6). Median survival was 6.6 versus 6.0 months (hazard ratio 0.86 [95% CI 0.66-1.12]; p=0.27), 1-year survival rate was 20% and 20%, progression-free survival rate at 6 months was 21.4% and 15.1% (p=0.13), respectively in TTF and active control patients. Responses were more common in the TTF arm (14% versus 9.6%, p=0.19). The TTF-related adverse events were mild (14%) to moderate (2%) skin rash beneath the transducer arrays. Severe adverse events occurred in 6% and 16% (p=0.022) of patients treated with TTF and chemotherapy, respectively. Quality of life analyses favored TTF therapy in most domains. Although no improvement in overall survival was demonstrated, the authors conclude that the efficacy and activity with this chemotherapy-free treatment device appears comparable to chemotherapy regimens that are commonly used for recurrent glioblastoma and that toxicity and quality of life favored TTF.

A treatment-based analysis of data from the pivotal phase III trial of the NovoTTF-100A System™ versus best physician's choice (BPC) chemotherapy was conducted by Kanner et al. (2014) in patients with recurrent glioblastoma multiforme (GBM), with particular focus on efficacy in patients using NovoTTF therapy as intended. Median overall survival (OS) was compared for recurrent GBM patients receiving at least one full cycle of treatment with NovoTTF-100A System or BPC chemotherapy (modified intention-to-treat [mITT] population). The relationship between NovoTTF-100A System compliance and OS was evaluated in the ITT population. Kaplan-Meier analyses examined treatment-related differences in OS for various patient subgroups. Median OS was significantly higher in patients receiving ≥1 course of NovoTTF therapy versus BPC (7.7 v 5.9 months; hazard ratio, 0.69; 95% confidence interval [CI], 0.52-0.91; P = .0093). Median OS was also significantly higher in patients receiving NovoTTF therapy with a maximal monthly compliance rate ≥75% (≥18 hours daily) versus those with a <75% compliance rate (7.7 v 4.5 months; P = .042), and Kaplan-Meier analysis demonstrated a significant trend for improved median OS with higher compliance (P = .039). Additional post hoc analysis showed significantly higher median OS with NovoTTF therapy than with BPC for patients with prior low-grade glioma, tumor size ≥18 cm(2), Karnofsky performance status ≥80, and those who had previously failed bevacizumab therapy. This contrasts with the equivalent efficacy reported previously based on analysis of all randomized ITT subjects, including many who did not receive a full cycle of treatment. The authors summarized that results from the present study suggest that when used as intended, NovoTTF Therapy provides efficacy superior to that of chemotherapy in a heterogeneous population of patients with recurrent GBM. Post hoc analyses identified subgroups of patients who may be particularly good candidates for NovoTTF Therapy, pending further confirmatory studies.

Wong et al., (2015) conducted a retrospective chart review from a single institution on patients treated with NovoTTF-100A and bevacizumab between November 2011 and December 2013. The patients were segregated into two cohorts: (i) those treated with NovoTTF-100A and bevacizumab only and (ii) those treated with NovoTTF-100A, bevacizumab and TCCC. Response to treatment was measured according to the Response Assessment in Neuro-Oncology criteria. Progression-free survival (PFS) and OS were measured from the time of application of these treatments to death or last follow up. The cohort treated with NovoTTF-100A, bevacizumab, and TCCC (n = 3) did not differ significantly from the rest of the cohort treated with NovoTTF-100A and bevacizumab only (n = 34). Potential reasons for this include baseline clinical characteristics and dexamethasone use. The authors note limitations with this review to be the number of patients treated with NovoTTF-100A, bevacizumab, and TCCC is small and therefore they cannot recommend this combination as standard clinical practice. However, they commented that the findings in their patients are notable and it can serve as a basis for future clinical trials. Second, it is unclear what the relative contribution of immunosuppression in the periphery versus the tumor microenvironment has on treatment resistance in recurrent glioblastomas. Therefore, they conclude that combination treatment, rather than single-agent monotherapy, will more likely affect meaningful clinical results.



Wong et al., (2014) analyzed the characteristics of responders and nonresponders in both cohorts of the phase III trial which compared NovoTTF-100A Best Physician's Choice (BPC) chemotherapy for recurrent glioblastoma to determine the characteristics of response and potential predictive factors. Their analysis showed that a significantly higher proportion of NovoTTF-100A responders, five of 14 (36%), had prior low-grade histologies while none of seven (0%) BPC responder had this type of histological characteristics, suggesting that secondary glioblastoma may be more responsive to NovoTTF-100A treatment. Because primary and secondary glioblastomas have different genetic alterations, notably EGFR and MDM2 amplifications together with p16 deletion in primary glioblastomas and mutation, IDH1 mutation and PDGFR amplification in secondary glioblastomas, the distinct genetic makeup in these two subtypes of glioblastomas could make secondary glioblastomas more susceptible to NovoTTF-100A treatment. Secondary glioblastomas and low dexamethasone usage are associated with a higher proportion of NovoTTF-100A responders but not BPC chemotherapy responders. The authors surmise that during treatment with NovoTTF-100A, this slower rate of tumor progression might allow enough time for the efficacy of TTFields to emerge because it may take multiple mitotic cycles to reduce the number of tumor cells and the size of the glioblastoma. The authors recommend that future clinical trials on the NovoTTF-100A device must include stratification of potential predictive factors of response that include both genetic and epigenetic determinants.

Mrugala et al., (2014) evaluated data collected from all adult patients with recurrent GBM who began commercial Novocure TTF therapy through the Patient Registry Dataset (PRiDe), which is a post-marketing registry of all recurrent GBM patients who received NovoTTF therapy in a real-world, clinical practice setting in the United States between 2011 and 2013. Data from 457 recurrent GBM patients who received Novocure TTF therapy in 91 US cancer centers were analyzed. More patients in PRiDe than the EF-11 trial received Novocure TTF therapy for first recurrence (33% v 9%) and had received prior bevacizumab therapy (55.1% v 19%). Median OS was significantly longer with Novocure TTF therapy in clinical practice (PRiDe data set) than in the EF-11 trial (9.6 v 6.6 months; HR, 0.66; 95% CI, 0.05 to 0.86, P = .0003). One- and 2-year OS rates were more than double for Novocure TTF therapy patients in PRiDe than in the EF-11 trial (1-year: 44% v 20%; 2-year: 30% v 9%). First and second versus third and subsequent recurrences, high Karnofsky performance status (KPS), and no prior bevacizumab use were favorable prognostic factors. No unexpected adverse events were detected in PRiDe. As in the EF-11 trial, the most frequent adverse events were mild to moderate skin reactions associated with application of the Novocure TTF therapy transducer arrays. The authors concluded that results from PRiDe, together with those previously reported in the EF-11 trial, indicate that Novocure TTF therapy offers clinical benefit to patients with recurrent GBM, has high patient tolerability and favorable safety profile in the real-world, clinical practice setting.

Rulseh et al., (2012) reported the long-term survival of patients with glioblastoma multiforme treated with tumor-treating fields in a small pilot study of 20 individuals. The inclusion criteria of the study included a KPS  $\geq 70\%$  and age  $\geq 18$  years, and the patients were divided into two groups. The first group consisted of 10 patients diagnosed with recurring GBM after failing temozolomide treatment that were treated with TTField therapy alone, and the second group consisted of 10 newly diagnosed GBM patients at least four weeks post radiation therapy (with adjuvant temozolomide) that received TTField therapy combined with maintenance temozolomide. The treatment duration in individual patients varied between one and one and a half years, and all histological samples were independently examined in two laboratories in two countries. Twenty percent of the participants in the pilot study (4 out of 20) survived until the time of their report, roughly seven years. The individuals showed no clinical or radiological signs of recurrence and were no longer receiving any treatment. The authors suggest that in order to increase the probability of response to TTField therapy and subsequent long term survival, TTField treatment should be continued even in the face of initial radiologic tumor growth.

There is a lack of published evidence from randomized controlled trials examining the long-term safety and effectiveness of TTF as a treatment for tumors other than GBM, including non-small cell lung, brain metastasis, pancreatic cancer, ovarian cancer and mesothelioma. .

### **NovoTAL™ Simulation System**

There is limited published clinical evidence related to the NovoTAL™ simulation system and insufficient data to support improved long-term health outcomes with its use. This includes a small case series (Connelly et al., 2016), human head model (Wenger et al., 2015) and a user group survey (Chaudry et al., 2015). A framework for the use of NovoTAL in treatment planning has been proposed by Trusheim et al. (2016).

### **U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

The Optune is categorized by the FDA as a stimulator, low electric field, tumor treatment; it is assigned product code NZK. Refer to the following website for additional information on supplemental FDA approvals for the Optune: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>. (Accessed September 15, 2017)

NovoTAL simulation software is not regulated by the FDA.



## CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for electric tumor treatment field therapy. Local Coverage Determinations (LCDs) do exist; see the LCDs for [Tumor Treatment Field Therapy \(TTFT\)](#). (Accessed July 31, 2017)

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## POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
11/01/2017	<ul style="list-style-type: none"><li>Updated coverage rationale; replaced reference to "TTF" (tumor treatment field) with "electric TTF"</li><li>Updated definitions; added instruction to check the definitions within the member benefit plan document that supersede the definitions [listed in the policy]</li><li>Updated supporting information to reflect the most current description of services, clinical evidence, and references</li><li>Archived previous policy version CS146.A</li></ul>



# ELECTRIC TUMOR TREATMENT FIELD THERAPY

Policy Number: 2018T0582C

Effective Date: November 1, 2018

[Instructions for Use](#) ⓘ

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## Related Commercial Policy

- [Clinical Trials](#)

## Community Plan Policy

- [Electric Tumor Treatment Field Therapy](#)

## COVERAGE RATIONALE

**The use of U.S. Food and Drug Administration (FDA) approved devices to generate electric tumor treatment fields (TTF) to treat newly diagnosed histologically-confirmed Supratentorial glioblastoma (known also as glioblastoma multiforme [GBM] or World Health Organization [WHO] grade IV astrocytoma) is proven and medically necessary when used according to FDA labeled indications, contraindications, warnings and precautions, and when ALL of the following criteria are met:**

- Initial treatment with radiation therapy has been completed; and
- Individual is receiving Temozolomide; and
- Individual has a Karnofsky Performance Status (KPS) score of  $\geq 60$ ; and
- Individual or caregiver has been trained and is willing and able to apply the device daily; and
- Individual is willing to wear the device at least 18 hours daily.

### **Recurrent GBM**

**The use of FDA approved devices to generate electric TTF is proven and medically necessary following radiologically-confirmed recurrence of GBM in the supratentorial region of the brain after initial chemotherapy and when ALL of the following criteria are met:**

- The device is used as a monotherapy
- Individual has a KPS score of  $\geq 60$ ; and
- Individual or caregiver has been trained and is willing and able to apply the device daily; and
- Individual is willing to wear the device at least 18 hours daily.

When all of the above criteria are met for either newly diagnosed or recurrent GBM, an initial 3 months of electric TTF therapy will be approved.

Subsequent approval(s) for continuation of electric TTF is based on:

- MRI scan has been performed  $\leq 2$ -4 months prior to request and documents no evidence of disease progression. ; and
- KPS score of  $\geq 60$ ; and
- Documentation that the individual has been wearing the device at least 18 hours daily.

**The use of devices to generate electric tumor treatment fields (TTF) is considered investigational, unproven, and not medically necessary when the criteria above are not met and for all other indications.**

The FDA has not approved the use of electric TTF devices for indications other than GBM. Further studies are needed to determine the safety and long-term efficacy of electric TTF therapy for other types of cancer.

**Computer software used for therapeutic radiology clinical treatment planning in conjunction with electric tumor treatment field (TTF) therapy is unproven and not medically necessary.**

There is insufficient evidence to establish the efficacy of these products in the long-term outcomes of patients receiving electric TTF therapy.



## DEFINITIONS

**Karnofsky Performance Status (KPS):** A standard way of measuring the ability of cancer patients to perform ordinary tasks. KPS scores range from 0 to 100; a higher score means a person is better able to carry out daily activities. For example, a KPS of 60 means a person requires occasional assistance, but is able to care for most of their personal needs. KPS may be used to determine a patient's prognosis, to measure changes in a patient's ability to function, or to decide if a patient could be included in a clinical trial (National Cancer Institute [NCI], 2018).

**Supratentorial:** The upper portion of the brain comprised of the cerebrum and the diencephalon (NCI, 2018).

**Temozolomide:** An oral alkylating chemotherapy drug used in the treatment of some brain cancers. It is a first-line treatment for glioblastoma (NCI, 2018).

## APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

CPT Code	Description
77299	Unlisted procedure, therapeutic radiology clinical treatment planning <i>CPT® is a registered trademark of the American Medical Association</i>
HCPCS Code	Description
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type

## DESCRIPTION OF SERVICES

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Alternating electrical fields within the human body that disrupt the rapid cell division exhibited by cancer cells, with the alternating electrical fields applied to the brain through transducer arrays placed on the scalp. TTF harness electric fields to arrest the proliferation of tumor cells and to destroy them. The TTF technology takes advantage of the special characteristics and geometrical shape of dividing cells, which make them susceptible to the effects of the alternating electric TTFields. These special fields alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used for a particular treatment is specific to the cell type being treated (e.g., 200kHz for GBM). In contrast, the TTFields have not been shown to have an effect on cells that are not undergoing division. Since most normal adult brain cells proliferate very slowly, if at all, they are hypothesized to be little affected by the TTFields (Novocure, 2018).

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The mainstay of treatment for GBM is surgery, followed by radiation and chemotherapy. The primary objective of surgery is to remove as much of the tumor as possible without injuring the surrounding healthy brain tissue needed for normal neurological function (such as motor skills, the ability to speak and walk, etc.). However, GBMs are surrounded by a zone of migrating, infiltrating tumor cells that invade surrounding tissues, making it impossible to ever remove the tumor entirely. Surgery provides the ability to reduce the amount of solid tumor tissue within the brain, remove those cells in the center of the tumor that may be resistant to radiation and/or chemotherapy and reduce intracranial pressure (American Association of Neurological Surgeons [AANS], 2018).



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## CLINICAL EVIDENCE

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline for Central Nervous System Cancers, anaplastic gliomas/glioblastoma, includes standard brain radiation therapy (RT) + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy for patients with good performance status and either methylated or unmethylated/indeterminate MGMT promoter status, in whom resection was not feasible with the following footnote: "Alternating electric field therapy is only an option for patients with supratentorial disease" (category 1). For recurrence of GBM (GLIO-5), the guideline includes consideration of alternating electric treatment fields for glioblastoma after surgery, radiation and chemotherapy (category 2B) (NCCN, 2018).

Stupp et al. (2017) reported final outcomes from the randomized, open-label trial of 695 patients with glioblastoma whose tumor was resected or biopsied and had completed concomitant radiochemotherapy (median time from diagnosis to randomization, 3.8 months) and Optune therapy. Of the 695 randomized patients (median age, 56 years; IQR, 48-63; 473 men [68%]), 637 (92%) completed the trial. Median progression-free survival from randomization was 6.7 months in the TTFields-temozolomide group and 4.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.52-0.76;  $P < .001$ ). Median overall survival was 20.9 months in the TTFields-temozolomide group vs 16.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76;  $P < .001$ ). Systemic adverse event frequency was 48% in the TTFields-temozolomide group and 44% in the temozolomide-alone group. Mild to moderate skin toxicity underneath the transducer arrays occurred in 52% of patients who received TTFields-temozolomide vs no patients who received temozolomide alone. In the final analysis of this randomized clinical trial of patients with glioblastoma who had received standard radiochemotherapy, the addition of TTFields to maintenance temozolomide chemotherapy vs maintenance temozolomide alone, resulted in statistically significant improvement in progression-free survival and overall survival. These results are consistent with the previous interim analysis.

In a secondary analysis of the Stupp et al. (2017) trial, Taphoorn et al. (2018) examined the association of TTFields therapy with progression-free survival and HRQoL among patients with glioblastoma. Of the 695 patients in the study, 639 (91.9%) completed the baseline HRQoL questionnaire. Of these patients, 437 (68.4%) were men; mean (SD) age, 54.8 (11.5) years. Health-related quality of life did not differ significantly between treatment arms except for itchy skin. Deterioration-free survival was significantly longer with TTFields for global health (4.8 vs 3.3 months;  $P < .01$ ); physical (5.1 vs 3.7 months;  $P < .01$ ) and emotional functioning (5.3 vs 3.9 months;  $P < .01$ ); pain (5.6 vs 3.6 months;  $P < .01$ ); and leg weakness (5.6 vs 3.9 months;  $P < .01$ ), likely related to improved progression-free survival. Time to deterioration, reflecting the influence of treatment, did not differ significantly except for itchy skin (TTFields worse; 8.2 vs 14.4 months;  $P < .001$ ) and pain (TTFields improved; 13.4 vs 12.1 months;  $P < .01$ ). Role, social, and physical



functioning were not affected by TTFields. The addition of TTFields to standard treatment with temozolomide for patients with glioblastoma results in improved survival without a negative influence on HRQoL except for more itchy skin, an expected consequence from the transducer arrays.

In a multinational, open-label, randomized phase III trial (EF-14 trial), Stupp et al. (2015) compared Optune in combination with temozolomide to temozolomide alone in 700 patients age 18 and over with newly diagnosed GBM. The interim report revealed that in the intent-to-treat population, patients treated with TTFields plus temozolomide showed a statistically significant increase in progression free survival (PFS), the primary endpoint, compared to temozolomide alone (median PFS 7.1 months versus 4.0 months, hazard ratio=0.62, p=0.0013). In the per-protocol population, patients treated with TTFields plus temozolomide demonstrated a statistically significant increase in OS, a powered secondary endpoint, compared to temozolomide alone (median OS 20.5 months versus 15.6 months, hazard ratio=0.64, p=0.0042). In the intent-to-treat population, the median OS was 19.6 months versus 16.6 months, respectively, hazard ratio=0.74 (p=0.0329). The two-year survival rate was 50 percent greater with TTFields plus temozolomide versus temozolomide alone: 43 percent versus 29 percent. The trial's independent data monitoring committee concluded that the study met its endpoints at its pre-specified interim analysis of the first 315 patients with 18 months or more of follow-up. The committee recommended that the trial be terminated early for success and that all control patients be offered TTFields therapy even prior to progression. In addition, the authors reported that the trial showed Optune could be safely combined with temozolomide. There was no significant increase in systemic toxicities from Optune reported in combination with temozolomide versus temozolomide alone. The most common adverse reaction from Optune treatment was mild to moderate skin irritation, which according to the authors was easily managed, reversible and did not result in treatment discontinuation. This clinical trial has some important limitations. Patient enrollment occurred only after the end of radiochemotherapy, leading to some variation in the delivery of standard treatment of temozolomide and radiotherapy. Patients who had progressed early during radiochemotherapy were not eligible for randomization, thus excluding patients with very poor prognoses. There is likely reporting bias for second-line therapies after tumor progression because in the TTFields plus temozolomide group, TTFields were to be continued, and thus, more detailed treatment information has been tracked for this group.

Stupp et al. (2012) completed a phase III randomized trial (EF-11 trial) of chemotherapy-free treatment of Novo tumor treatment fields (TTF) (20-24h/day) versus active chemotherapy in the treatment of patients with recurrent glioblastoma. The primary end-point was improvement of overall survival. Patients (median age 54 years (range 23-80), Karnofsky performance status 80% (range 50-100) were randomized to TTF alone (n=120) or active chemotherapy control (n=117). Number of prior treatments was two (range 1-6). Median survival was 6.6 versus 6.0 months (hazard ratio 0.86 [95% CI 0.66-1.12]; p=0.27), 1-year survival rate was 20% and 20%, progression-free survival rate at 6 months was 21.4% and 15.1% (p=0.13), respectively in TTF and active control patients. Responses were more common in the TTF arm (14% versus 9.6%, p=0.19). The TTF-related adverse events were mild (14%) to moderate (2%) skin rash beneath the transducer arrays. Severe adverse events occurred in 6% and 16% (p=0.022) of patients treated with TTF and chemotherapy, respectively. Quality of life analyses favored TTF therapy in most domains. Although no improvement in overall survival was demonstrated, the authors conclude that the efficacy and activity with this chemotherapy-free treatment device appears comparable to chemotherapy regimens that are commonly used for recurrent glioblastoma and that toxicity and quality of life favored TTF.

A treatment-based analysis of data from the pivotal phase III trial of the NovoTTF-100A System™ versus best physician's choice (BPC) chemotherapy was conducted by Kanner et al. (2014) in patients with recurrent glioblastoma multiforme (GBM), with particular focus on efficacy in patients using NovoTTF therapy as intended. Median overall survival (OS) was compared for recurrent GBM patients receiving at least one full cycle of treatment with NovoTTF-100A System or BPC chemotherapy (modified intention-to-treat [mITT] population). The relationship between NovoTTF-100A System compliance and OS was evaluated in the ITT population. Kaplan-Meier analyses examined treatment-related differences in OS for various patient subgroups. Median OS was significantly higher in patients receiving ≥1 course of NovoTTF therapy versus BPC (7.7 v 5.9 months; hazard ratio, 0.69; 95% confidence interval [CI], 0.52-0.91; P = .0093). Median OS was also significantly higher in patients receiving NovoTTF therapy with a maximal monthly compliance rate ≥75% (≥18 hours daily) versus those with a <75% compliance rate (7.7 v 4.5 months; P = .042), and Kaplan-Meier analysis demonstrated a significant trend for improved median OS with higher compliance (P = .039). Additional post hoc analysis showed significantly higher median OS with NovoTTF therapy than with BPC for patients with prior low-grade glioma, tumor size ≥18 cm(2), Karnofsky performance status ≥80, and those who had previously failed bevacizumab therapy. This contrasts with the equivalent efficacy reported previously based on analysis of all randomized ITT subjects, including many who did not receive a full cycle of treatment. The authors summarized that results from the present study suggest that when used as intended, NovoTTF Therapy provides efficacy superior to that of chemotherapy in a heterogeneous population of patients with recurrent GBM. Post hoc analyses identified subgroups of patients who may be particularly good candidates for NovoTTF Therapy, pending further confirmatory studies.

Wong et al, (2015) conducted a retrospective chart review from a single institution on patients treated with NovoTTF-100A and bevacizumab between November 2011 and December 2013. The patients were segregated into two cohorts:



(i) those treated with NovoTTF-100A and bevacizumab only and (ii) those treated with NovoTTF-100A, bevacizumab and TCCC. Response to treatment was measured according to the Response Assessment in Neuro-Oncology criteria. Progression-free survival (PFS) and OS were measured from the time of application of these treatments to death or last follow up. The cohort treated with NovoTTF-100A, bevacizumab, and TCCC ( $n = 3$ ) did not differ significantly from the rest of the cohort treated with NovoTTF-100A and bevacizumab only ( $n = 34$ ). Potential reasons for this include baseline clinical characteristics and dexamethasone use. The authors note limitations with this review to be the number of patients treated with NovoTTF-100A, bevacizumab, and TCCC is small and therefore they cannot recommend this combination as standard clinical practice. However, they commented that the findings in their patients are notable and it can serve as a basis for future clinical trials. Second, it is unclear what the relative contribution of immunosuppression in the periphery versus the tumor microenvironment has on treatment resistance in recurrent glioblastomas. Therefore, they conclude that combination treatment, rather than single-agent monotherapy, will more likely affect meaningful clinical results.

Wong et al. (2014) analyzed the characteristics of responders and nonresponders in both cohorts of the phase III trial which compared NovoTTF-100A Best Physician's Choice (BPC) chemotherapy for recurrent glioblastoma to determine the characteristics of response and potential predictive factors. Their analysis showed that a significantly higher proportion of NovoTTF-100A responders, five of 14 (36%), had prior low-grade histologies while none of seven (0%) BPC responder had this type of histological characteristics, suggesting that secondary glioblastoma may be more responsive to NovoTTF-100A treatment. Because primary and secondary glioblastomas have different genetic alterations, notably *EGFR* and *MDM2* amplifications together with *p16* deletion in primary glioblastomas and mutation, *IDH1* mutation and *PDGFR* amplification in secondary glioblastomas, the distinct genetic makeup in these two subtypes of glioblastomas could make secondary glioblastomas more susceptible to NovoTTF-100A treatment. Secondary glioblastomas and low dexamethasone usage are associated with a higher proportion of NovoTTF-100A responders but not BPC chemotherapy responders. The authors surmise that during treatment with NovoTTF-100A, this slower rate of tumor progression might allow enough time for the efficacy of TTFs to emerge because it may take multiple mitotic cycles to reduce the number of tumor cells and the size of the glioblastoma. The authors recommend that future clinical trials on the NovoTTF-100A device must include stratification of potential predictive factors of response that include both genetic and epigenetic determinants.

Mrugala et al. (2014) evaluated data collected from all adult patients with recurrent GBM who began commercial Novocure TTF therapy through the Patient Registry Dataset (PRiDe), which is a post-marketing registry of all recurrent GBM patients who received NovoTTF therapy in a real-world, clinical practice setting in the United States between 2011 and 2013. Data from 457 recurrent GBM patients who received Novocure TTF therapy in 91 US cancer centers were analyzed. More patients in PRiDe than the EF-11 trial received Novocure TTF therapy for first recurrence (33% v 9%) and had received prior bevacizumab therapy (55.1% v 19%). Median OS was significantly longer with Novocure TTF therapy in clinical practice (PRiDe data set) than in the EF-11 trial (9.6 v 6.6 months; HR, 0.66; 95% CI, 0.05 to 0.86,  $P = .0003$ ). One- and 2-year OS rates were more than double for Novocure TTF therapy patients in PRiDe than in the EF-11 trial (1-year: 44% v 20%; 2-year: 30% v 9%). First and second versus third and subsequent recurrences, high Karnofsky performance status (KPS), and no prior bevacizumab use were favorable prognostic factors. No unexpected adverse events were detected in PRiDe. As in the EF-11 trial, the most frequent adverse events were mild to moderate skin reactions associated with application of the Novocure TTF therapy transducer arrays. The authors concluded that results from PRiDe, together with those previously reported in the EF-11 trial, indicate that Novocure TTF therapy offers clinical benefit to patients with recurrent GBM, has high patient tolerability and favorable safety profile in the real-world, clinical practice setting.

Rulseh et al. (2012) reported the long-term survival of patients with glioblastoma multiforme treated with tumor-treating fields in a small pilot study of 20 individuals. The inclusion criteria of the study included a KPS  $\geq 70\%$  and age  $\geq 18$  years, and the patients were divided into two groups. The first group consisted of 10 patients diagnosed with recurring GBM after failing temozolomide treatment that were treated with TTF therapy alone, and the second group consisted of 10 newly diagnosed GBM patients at least four weeks post radiation therapy (with adjuvant temozolomide) that received TTF therapy combined with maintenance temozolomide. The treatment duration in individual patients varied between one and one and a half years, and all histological samples were independently examined in two laboratories in two countries. Twenty percent of the participants in the pilot study (4 out of 20) survived until the time of their report, roughly seven years. The individuals showed no clinical or radiological signs of recurrence and were no longer receiving any treatment. The authors suggest that in order to increase the probability of response to TTF therapy and subsequent long term survival, TTF treatment should be continued even in the face of initial radiologic tumor growth.

There is a lack of published evidence from randomized controlled trials examining the long-term safety and effectiveness of TTF as a treatment for tumors other than GBM, including non-small cell lung, brain metastasis, pancreatic cancer, ovarian cancer and mesothelioma.



## **NovoTAL™ Simulation System**

There is limited published clinical evidence related to the NovoTAL™ simulation system, and insufficient data to support improved long-term health outcomes with its use. This includes a small case series (Connelly et al., 2016), human head model (Wenger et al., 2015), and a user group survey (Chaudry et al., 2015). A framework for the use of NovoTAL in treatment planning has been proposed by Trusheim et al. (2016).

## **U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

The Optune is categorized by the FDA as a stimulator, low electric field, tumor treatment; see the following website for the initial Premarket Approval information:

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100034S013>. (Accessed July 5, 2018)

Refer to the following website for additional information on supplemental FDA approvals for the Optune using product code NZK: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpMA/pma.cfm>. (Accessed July 16, 2018)

NovoTAL simulation software is not regulated by the FDA.

## **CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)**

Medicare does not have a National Coverage Determination (NCD) for electric tumor treatment field therapy. Local Coverage Determinations (LCDs) exist, see the LCDs for [Tumor Treatment Field Therapy \(TTFT\)](#). (Accessed June 12, 2018)

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## POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
11/01/2018	<ul style="list-style-type: none"> <li>Reorganized policy template: <ul style="list-style-type: none"> <li>Simplified and relocated <i>Instructions for Use</i></li> <li>Removed <i>Benefit Considerations</i> section</li> </ul> </li> <li>Revised coverage rationale: <p><b>Newly diagnosed histologically-confirmed Supratentorial glioblastoma [known also as glioblastoma multiforme (GBM)]</b></p> <ul style="list-style-type: none"> <li>Added language to clarify guidelines apply to <i>newly diagnosed</i> Supratentorial glioblastoma</li> <li>Removed language indicating this service is proven/medically necessary "as adjunctive therapy" [when criteria is met]</li> <li>Modified coverage criteria: <ul style="list-style-type: none"> <li>Replaced criterion requiring "initial treatment with <i>debulking surgery or biopsy followed by chemoradiation with concomitant Temozolomide and radiotherapy</i> has been completed" with "initial treatment with <i>radiation therapy</i> has been completed"</li> <li>Added criterion requiring the individual is receiving Temozolomide</li> </ul> </li> </ul> <p><b>Recurrent GBM</b></p> <ul style="list-style-type: none"> <li>Added language to indicate: <ul style="list-style-type: none"> <li>The use of FDA approved devices to generate electric tumor treatment fields (TTF) is proven and medically necessary following radiologically-confirmed recurrence of GBM in the supratentorial region of the brain after initial chemotherapy and when all of the following criteria are met: <ul style="list-style-type: none"> <li>The device is used as a monotherapy; and</li> <li>Individual has a KPS score of &gt;60; and</li> <li>Individual or caregiver has been trained and is willing and able to apply the device daily; and</li> <li>Individual is willing to wear the device at least 18 hours daily</li> </ul> </li> <li>When all of the criteria [listed in the policy] are met for recurrent GBM, an initial 3 months of electric TTF therapy will be approved</li> </ul> </li> <li>Modified coverage criteria for continuation of electric TTF therapy to indicate subsequent approval is based on: <ul style="list-style-type: none"> <li>MRI scan has been performed &lt;2-4 months prior to request and documents no evidence of disease progression; and</li> <li>KPS score of &gt;60; and</li> <li>Documentation that the individual has been wearing the device at least 18 hours daily</li> </ul> </li> </ul> </li> <li>Updated supporting information to reflect the most current clinical evidence, FDA information, and references</li> <li>Archived previous policy version 2017T0582B</li> </ul>



## INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.



# MEDICAL POLICY

<b>SUBJECT: TUMOR–TREATMENT FIELD THERAPY FOR GLIOBLASTOMA</b>	<b>EFFECTIVE DATE: 05/28/15 REVISED DATE: 08/18/16, 08/17/17, 04/19/18</b>
<b>POLICY NUMBER: 6.01.45 CATEGORY: Technology Assessment</b>	<b>PAGE: 1 OF: 5</b>
<ul style="list-style-type: none"><li>• <i>If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.</i></li><li>• <i>If a commercial product, including an Essential Plan product, covers a specific service, medical policy criteria apply to the benefit.</i></li><li>• <i>If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.</i></li></ul>	

## POLICY STATEMENT:

- I. Based upon our criteria and assessment of peer-reviewed literature, alternating electrical field therapy (Tumor-Treatment Field (TTF) therapy) using Optune® (Novocure Inc, Portsmouth, New Hampshire) for treatment of recurrent Glioblastoma multiforme (GBM) is considered **medically appropriate** when all of the following criteria have been met:
  - A. 1<sup>st</sup> or 2<sup>nd</sup> recurrence of GBM; and
  - B. The individual has a Karnofsky Performance Status (KPS) of 90 or greater; and
  - C. The individual has not received prior treatment with Bevacizumab; and
  - D. The device is to be used as monotherapy after failure of standard medical therapy (e.g., chemotherapy, surgery, and radiation therapy).
  - E. There is documented evidence the member is compliant with the TTF device during a one month trial period. Compliance is defined as use of the device for 18 hours or more per day during the one month trial period.
- II. Based upon our criteria and assessment of peer-reviewed literature, alternating electrical field therapy (Tumor-Treatment Field (TTF) therapy) using Optune® (Novocure Inc, Portsmouth, New Hampshire) for treatment of newly diagnosed Glioblastoma multiforme (GBM) is considered **medically appropriate** when the following criteria have been met:
  - A. The device is to be used as an adjunct with the chemotherapy drug temozolomide (TMZ); and
  - B. Following standard treatments that include maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

## POLICY GUIDELINES:

- I. The Optune® (Novocure Inc, Portsmouth, New Hampshire) will be allowable for up to 6 months if the patient is compliant with the regimen. Continued use after 6 months will require additional documentation to show no progression in the patient's condition.
- II. The Optune® (Novocure Inc, Portsmouth, New Hampshire) is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM).
- III. The Optune® (Novocure Inc, Portsmouth, New Hampshire) was approved by the U.S. Food and Drug Administration (FDA) in April 2011 to deliver TTF therapy and is intended as a treatment for adult patients (22 years of age or older) with confirmed glioblastoma multiforme, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment, and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted.
- IV. The Optune® (Novocure Inc, Portsmouth, New Hampshire) was approved by the U.S. Food and Drug Administration (FDA) in October 2015 to deliver TTF therapy and is intended as a treatment for adult patients (22 years of age or older) with newly-diagnosed glioblastoma multiforme when given along with the chemotherapy drug temozolomide following standard treatments that include surgery, and radiation therapy and chemotherapy used together.
- V. The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.



<b>SUBJECT: TUMOR–TREATMENT FIELD THERAPY FOR GLIOBLASTOMA</b>  <b>POLICY NUMBER: 6.01.45</b> <b>CATEGORY: Technology Assessment</b>	<b>EFFECTIVE DATE: 05/28/15</b> <b>REVISED DATE: 08/18/16, 08/17/17, 04/19/18</b>  <b>PAGE: 2 OF: 5</b>
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## **DESCRIPTION:**

Glioblastoma multiforme (GBM) is the most common and aggressive primary intracranial tumor with approximately 33% surviving 1 year and less than 5% surviving more than 5 years. Median survival with optimal therapy has been reported to be 10-15 months with most tumors recurring within 7-9 months despite multimodal treatment (e.g. repeat surgery, re-irradiation and chemotherapy). Choice of chemotherapy for treatment in the case of recurrence varies but may include alkylating agents (e.g., lomustine, carmustine, procarbazine), re-treatment with temozolomide, and more recently, bevacizumab either alone or in combination with other agents. Overall survival after recurrence is relatively short even with optimal therapy. New or novel treatments such as TTF therapy are being investigated to improve survival in patients with GBM.

TTF therapy is delivered via the Optune® (Novocure Inc, Portsmouth, New Hampshire) which is a battery-powered, portable device that generates alternating low intensity, intermediate electrical fields (100-300 kHz) by four disposable electrode arrays (replaced 1-2 times per week) that are noninvasively attached to the patient's shaved scalp placed in such a way to encompass the tumor. The alternating low intensity electrical field is thought to disrupt cell division of the cancer cells so that either cell division does not occur or it is ineffective, resulting in death of the cancer cells without harming the normal healthy cells. The device is used by the patient at home on a continuous basis (20-24 h/d) for the duration of treatment, which can last for several months. Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living.

## **RATIONALE:**

The Food and Drug Administration approval of the Optune® device formally NovoTTF-100A system was based on a phase 3, multinational prospective RCT (Stupp et al, 2012). Two hundred thirty-seven patients with relapsed or progressive glioblastoma multiforme (GBM), despite conventional radiotherapy were randomized in a 1:1 ratio to receive TTF therapy (delivered by the NovoTTF-100A System) only (n=120) or the best standard of care chemotherapy (active control) (n=117). The choice of chemotherapy regimens varied, reflecting local practice at each of the 28 participating clinical centers which were across 7 countries. Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky Performance Status (KPS) score of 80%. More than 80% of participants had failed 2 or more prior chemotherapy regimens, and 20% had failed bevacizumab prior to study enrollment. Ninety-seven percent (116) of 120 participants in the TTF group started treatment and 93 participants (78%) completed 1 cycle (4 weeks) of therapy. Discontinuation of TTF therapy occurred in 27 participants (22%) due to noncompliance or the inability to handle the device. For each TTF treatment month, the median compliance was 86% (range, 41%-98%), which equaled a mean use of 20.6 hours per day. In the active control group, 113 (97%) of the 117 assigned participants received chemotherapy and all except 1 individual completed a full treatment course. Twenty-one participants (18%) in the active control group did not return to the treating site and details on disease progression and toxicity were not available. This RCT did not reach its primary end point of improved survival compared with active chemotherapy. With a median follow-up of 39 months, 220 participants (93%) had died. Median survival was 6.6 months in the TTF group compared with 6.0 months in the active control group (hazard ratio, 0.86; 95% confidence interval [CI], 0.66 to 1.12; p=0.27). For both groups, 1-year survival was 20%. The survival rates for 2- and 3-year survival were 8% and 4%, respectively, for the TTF group versus 5% and 1%, respectively, for the active control group. PFS rate at 6 months was 21.4% in the TTF group, compared with 15.1% in the active control group (p=0.13). Objective radiologic responses (partial and complete response) were noted in 14 participants in the TTF group and 7 in the active control group, with a calculated response rate of 14.0% (95% CI, 7.9% to 22.4%) versus 9.6% (95% CI, 3.9% to 18.8%), respectively. Sixteen percent of the TTF participants had grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids. Active control participants experienced grade 2-4 events by organ system related to the pharmacologic activity of chemotherapy agents used; severe (grades 3 and 4) toxicity was observed in 3% of participants. Longitudinal quality of life (QOL) data were available in 63 participants (27%). There were no meaningful differences observed between the groups in the domains of global health and social functioning. However, cognitive, emotional, and role functioning favored TTF therapy, whereas physical functioning favored chemotherapy. Symptom scale analysis was in accordance to treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the TTF group. In summary, this RCT failed to demonstrate the primary end point of improved survival with



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TTF therapy in comparison to chemotherapy. Limitations of the trial included a somewhat heterogeneous patient population, with participants included after progression of 1 or several lines of chemotherapy, as well as the use of different chemotherapy regimens in the control group. Another limitation is the absence of a placebo/supportive care arm. In the setting of advanced disease, the supportive care arm would have been useful to gauge the safety and efficacy of treatment for both groups of patients. Treatments used in the active control arm (best standard of care chemotherapy) in the recurrent disease setting have previously demonstrated limited efficacy, thus limiting the ability to determine the true treatment effect of TTF. Data from a trial of TTF versus placebo, or TTF plus standard chemotherapy versus standard chemotherapy alone would therefore provide a better assessment of treatment efficacy.

A subgroup analysis of patient data of this phase 3 trial (Wong et al, 2014) evaluated the different characteristics of responders and nonresponders in the TTF group compared to the active control group. More patients in the TTF arm were considered responders (14/120 vs 7/117 in the chemotherapy arm.) Median response time was longer for those in the TTF arm than the chemotherapy arm (7.3 months vs 5.6 months,  $p<0.001$ ), and there was a strong correlation (Pearson's  $r$ ) between response and OS in the TTF arm ( $p<0.001$ ) but not in chemotherapy arm ( $p=0.29$ ). Compared with the chemotherapy arm, a higher proportion of responders in the TTF arm had a prior low-grade histology (36% vs 0%). These differences in treatment responder groups suggest that TTF therapy may differentially benefit certain types of GBM; however, the small numbers of responders in both groups limits generalizations that can be drawn from this analysis.

Analysis of the NovoTTF-100A™ Patient Registry Dataset (PRiDe) of 457 patients with recurrent GBM who were treated with NovoTTF therapy in the United States between October 2011 and November 2013 and comparison to patient data in the Phase 3 trial was performed (Mrugula et al 2014) to provide a larger dataset of patients with recurrent GBM treated with TTF therapy. No new adverse events in the PRiDe group of patients were reported compared to the Phase 3 trial group. However median overall survival was longer in the TTF group in the PriDe group (9.6 months) compared to the TTF group in the Phase 3 trial (6.6 months) or in the active chemotherapy group (6.0 months). Median treatment time was almost double for the TTF PriDe group compared to either the TTF or chemotherapy group in the Phase 3 trial. Favorable prognostic factors in the PriDe group included 75% or more daily compliance of the device, treatment with TTF at first recurrence, no prior treatment with bevacizumab, and Karnofsky Performance Score (KPS) 90 or greater. The authors suggest there are subsets of patients who derive significant benefit from TTF therapy and that TTF therapy using the NovoTTF-100A™ device is safe and efficacious to treat recurrent GBM.

The Food and Drug Administration approval of the Optune® device formally NovoTTF-100A system for newly diagnosed glioblastoma multiforme (GBM) was based on the results from a clinical trial involving 695 patients newly diagnosed with GBM that compared those who used the device with temozolomide (TMZ) to those receiving TMZ alone (Stupp, 2015). Patients who used the device along with TMZ lived, on average, about 7 months with no disease progression compared to 4 months for those who had the drug alone. The device plus TMZ group survived for an average of 19.4 months after starting treatment compared to 16.6 months for those who were treated with TMZ alone.

The use of TTF therapy has been described in a number of case series. However, without evidence from additional high quality comparative studies, these studies provide limited additional evidence about whether TTF therapy improves outcomes compared with currently available therapy for GBM.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Central Nervous System (v 1.2016) states that alternating electrical field therapy for glioblastoma may be considered as a treatment option for recurrent disease (Category 2A).



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**CODES:**      Number      Description

*Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).

**CPT:**            There are no specific CPT codes for tumor treatment field therapy.

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**HCPCS:**        A4555            Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only

                     E0766            Electrical stimulation device used for cancer treatment, includes all accessories, any type

**ICD10:**        C71.0-C71.9    Malignant neoplasm of brain (code range)

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\* key article

#### **KEY WORDS:**

Electric field therapy, NovoTTF-100A, glioblastoma.

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## **CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS**

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There is currently a Local Coverage Determination (LCD) for Tumor Treatment Field Therapy. Please refer to the following LCD website for Medicare Members: [https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34823&ver=14&CtrctrSelected=389\\*1&Ctrctr=38you do finger9&s=41&DocType=Active&bc=AggAAAIAlAAAAA%3d%3d&](https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34823&ver=14&CtrctrSelected=389*1&Ctrctr=38you do finger9&s=41&DocType=Active&bc=AggAAAIAlAAAAA%3d%3d&)



# TUMOR TREATMENT FIELDS

[Benefit Application](#)

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[Policy](#)

[Procedure Codes](#)

[Selected References](#)

[Policy History](#)

Medical Policy: 06.01.34

Original Effective Date: November 2014

Reviewed: October 2018

Revised: October 2018

## **BENEFIT APPLICATION:**

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

This Medical Policy document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged or new medical literature may have been published. This Medical Policy will be reviewed regularly and be updated as scientific and medical literature becomes available.

## **DESCRIPTION:**

Glioblastoma is the most aggressive cancer that begins within the brain. Due to its multiple forms, it is also termed Glioblastoma multiforme (GBM). According to its location in the brain it may also give rise to hemiparesis, seizures, memory or speech impairment and visual changes. It is found to be more common in males than females. Currently there is no known cure but treatments are available. Tumor treatment fields (TTF) (e.g. Optune® device) is one such treatment that aims to prolong progression-free survival (PFS) and overall survival (OS).



Optune® (formerly NovoTTF-100A System) is the only legally marketed TTF delivery system available in the United States. The system used for the therapy consists of the Optune® Treatment Kit (Novocure, Ltd.) and INE Transducer Arrays. The kit includes the Electric Field Generator (NovoTTF-100A/Optune® device), power supply, portable battery, battery rack, battery charger, connection cable, and carrying case. The arrays are packaged with a gel layer, padding, medical tape, and overlapping liner. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process. The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed glioblastoma multiforme (GBM), following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved Novocure's request for a product name change from NovoTTF-110A System to Optune®.

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM. The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune® with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

The mechanism of action as described by the manufacturer: Tumor treating fields (TTF)/Electric tumor treatment fields is a locally or regionally delivered treatment that produces electric fields within the human body to disrupt the rapid cell division exhibited by cancer cells. TTF therapy works by creating alternating, "wave-like" electric fields that travel across their region of usage in different directions. Because structures within dividing cells have an electric charge, they interact with these electric fields.

## **MAPPING SOFTWARE TO OPTIMIZE TTF THERAPY (E.G. NOVOTAL™ SIMULATION SYSTEM)**



The NovoTAL™ (Transducer Array Layout) System (Novocure Inc.) is a proprietary software tool that produces a custom transducer array layout to optimize Optune therapy for each patient. According to the manufacturer of Optune® (TTF) that also developed the NovoTAL™ Simulation System: To ensure patients receive the maximal therapeutic level of TTFields at the site of their tumor, tumor burden is mapped and an optimal array layout is personalized using the NovoTAL software. The NovoTAL software utilizes magnetic resonance imaging (MRI) measurements for head size and tumor location obtained from axial and coronal T1 post contrast sequences to determine the optimal paired transducer array configuration that will deliver the maximal field intensity at the site of the tumor.

## **NEWLY DIAGNOSED GBM**

The primary treatment for glioblastoma multiforme (GBM) is debulking surgery to remove as much of the tumor as possible. At that time, some patients may undergo implantation of the tumor cavity with a carmustine (bis chloroethylnitrosourea [BCNU]) - impregnated wafer. Depending on the patient's physical condition, adjuvant radiation therapy, chemotherapy (typically temozolomide), or a combination of the 2 are given. After adjuvant therapy, some patients may undergo maintenance therapy with temozolomide.

In the adjuvant setting, Optune® demonstrated an improvement in overall survival (OS) when combined with temozolomide, when compared with the chemotherapy agent alone. In an analysis of 695 patients enrolled in the phase III EF-14 study, the median OS was 19.4 months with Optune® compared with 16.6 months with temozolomide alone. Additionally, progression-free survival (PFS) was improved by approximately 3 months, according to the FDA.

## **RECURRENT GBM**

Treatment of GBM is rarely curative, and tumors will recur in mostly all patients.

No standard treatment exists for recurrent GBM. In patients with disease that recurs after initial treatment, additional debulking surgery may be used if recurrence is localized. Other treatment options for recurrent disease include various forms of systemic medications such as bevacizumab, bevacizumab plus chemotherapy (e.g., irinotecan, bis-chloroethylnitrosourea/chloroethylnitrosourea, temozolomide), temozolomide, nitrosourea, procarbazine plus chloroethylnitrosourea and vincristine), cyclophosphamide, and platinum-based agents.

Clinical studies are ongoing to determine the safety and efficacy of TTF therapy as part of combination therapy for treating recurrent GBM. TTF therapy is under investigation as a combination therapy with chemotherapy plus bevacizumab and as a combination therapy with chemotherapy after irradiation therapy for treating recurrent GBM.

## **TREATMENT OUTSIDE OF GLIOBLASTOMA**

Tumor treating fields technology (TTF) is also being studied as a treatment for other solid tumors (e.g., melanoma, pancreatic adenocarcinoma and non-small cell lung cancer). However, there is a lack of published evidence from randomized controlled trials examining the long-term safety and effectiveness of TTF as a treatment of these cancers at this time.

## **GUIDELINES AND POSITION STATEMENTS**



## **THE NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)**

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on Central Nervous Systems Tumors (v.1.2018) recommend TTF therapy in conjunction with standard brain radiation therapy and current/adjuvant temozolomide for patients with supratentorial disease with good performance status. The panel conceded that data regarding TTF therapy is limited to evidence from the RCT which demonstrated similar survival in between groups. In addition, in the background section, the panel indicated that TTF therapy may be considered as a treatment option for recurrent GBM but not all panelists recommend treatment for these patients due to a lack of efficacy. The NCCN guideline does not advocate for the use of TTF therapy in the recommendation section for patients with recurrent disease.

## **KARNOFSKY PERFORMANCE STATUS SCORE**

A 10 point scale used by healthcare providers to quickly evaluate how an individual is feeling. This scale is used within the clinical guidelines algorithm.

- 100 Able to work. Normal; No complaints; No evidence of disease.
- 90 Able to work. Able to carry on normal activity; Minor symptoms.
- 80 Able to work. Normal activity with effort; some symptoms.
- 70 Independent; not able to work. Cares for self; Unable to carry on normal activity.
- 60 Disabled; dependent. Requires occasional assistance; cares for most needs.
- 50 Moderately disabled; dependent. Requires considerable assistance and frequent care.
- 40 Severely disabled; dependent. Requires special care and assistance.
- 30 Severely disabled. Hospitalized, death not imminent.
- 20 Very sick. Active supportive treatment needed.
- 10 Moribund. Fatal processes are rapidly progressing

## **EUROPEAN ASSOCIATION OF NEURO-ONCOLOGY (EANO)**

EANO Guideline on the Diagnosis and Treatment of Anaplastic Gliomas and Glioblastoma. 2014. This guideline states: "new approaches of glioma therapy... device based therapies such as tumor-treating fields should only be administered in the context of clinical trials."

## **EUROPEAN SOCIETY OF MEDICAL ONCOLOGY (ESMO)**

High-grade Glioma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. 2014. This guideline states: "Applying alternating electric fields—tumor-treating fields—using a battery powered device connected to electrodes placed on the patient's scalp—was compared with physicians' choice of chemotherapy in a randomized trial in recurrent disease. TTF failed to prolong survival compared with second-line chemotherapy [I, A]." This guideline defines Level of Evidence I as "evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity." This guideline defines Grade of Recommendation A as "strong evidence for efficacy with a substantial clinical benefit, strongly recommended."

Some clinical researchers assert that TTF "could be further evaluated in combination with chemotherapy, as a maintenance treatment, or as a salvage therapy if radiotherapy or surgery is not possible." Clinical studies are ongoing to determine the safety and efficacy of TTF therapy as part of combination therapy for treating recurrent GBM. TTF therapy is under investigation as a combination therapy with chemotherapy plus bevacizumab and as a combination therapy with chemotherapy after irradiation therapy for treating recurrent GBM.

## **NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE)**



Guideline Brain Tumours (primary) and Brain Metastases in Adults (2018) This guideline manages suspected and confirmed glioma, suspected and confirmed meningioma, and suspected and confirmed brain metastases. It does not mention the use of tumor treatment fields.

## NATIONAL CANCER INSTITUTE (NIH)

### ADULT CENTRAL NERVOUS SYSTEM TUMORS TREATMENT (PDQ®)—HEALTH PROFESSIONAL VERSION-GLIOBLASTOMA TREATMENT

For patients with glioblastoma (WHO grade IV), the cure rate is very low with standard local treatment.

Standard treatment options for patients with newly diagnosed glioblastoma include the following:

1. Surgery plus radiation therapy and chemotherapy.
2. Surgery plus radiation therapy.
3. Carmustine-impregnated polymer implanted during initial surgery.
4. Radiation therapy and concurrent chemotherapy.

The standard treatment for patients with newly diagnosed glioblastoma is surgery followed by concurrent radiation therapy and daily temozolomide, and then followed by six cycles of temozolomide. The addition of bevacizumab to radiation therapy and temozolomide did not improve overall survival (OS).

The use of TTF is not mentioned within the information provided in the treatment section for Glioblastoma.

## DEFINITIONS

**Supratentorial** - the supratentorial region of the brain is the area located above the tentorium cerebelli. The area of the brain below the tentorium cerebelli is the infratentorial region. The supratentorial region contains the cerebrum, while the infratentorial region contains the cerebellum.

## PRIOR APPROVAL:

Not applicable.

## POLICY:

Tumor treating fields (TTF) therapy (e.g. Optune®) to treat glioblastoma multiforme is considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in patients with **newly** diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and chemotherapy when ALL of the following conditions are met:

- Adult patients ≥22 years of age **AND**
- Histologically-confirmed glioblastoma multiforme supratentorial tumor **AND**
- Karnofsky Performance Status score ≥60% **AND**
- Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (at least 18 hours of use per day) **AND**
- Lack of implanted medical devices, including but not limited to: spinal cord stimulators, pacemakers, defibrillators, and programmable shunts.



Tumor treatment fields (TTF) therapy to treat glioblastoma is considered **investigational**, including but not limited to the following:

- As an adjunct to standard medical therapy (eg, bevacizumab, chemotherapy) for patients with **progressive or recurrent** glioblastoma multiforme OR
- As an alternative to standard medical therapy for patients with **progressive or recurrent** glioblastoma multiforme OR
- For brain metastases OR
- For cancer in other areas of the brain.

The use of tumor treatment fields (TTF) therapy to treat all other types of cancer is considered **investigational**.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy.

## PROCEDURE CODES AND BILLING GUIDELINES:

To report provider services, use appropriate CPT\* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or diagnosis codes.

- E0766 Electrical stimulation device, used for cancer treatment, includes all accessories, any type
- A4555 Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only

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## POLICY HISTORY:

- October 2018 - Annual Review, Policy Revised
- October 2017 - Annual Review, Policy Revised
- October 2016 - Annual Review, Policy Revised
- October 2015 - Annual Review, Policy Revised
- November 2014 - New Policy

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# TUMOR TREATING FIELDS TECHNOLOGY: ALTERNATING ELECTRIC FIELD THERAPY FOR THE TREATMENT OF SOLID TUMORS

LAURA BENSON

**OBJECTIVE:** *To provide an overview of Tumor Treating Fields (TTFields) and the Optune device in the treatment of glioblastoma multiforme as well as discuss the evolution of TTFields technology for the treatment of different tumor types.*

**DATA SOURCES:** *Peer reviewed publications, proceedings, and Internet-based resources.*

**CONCLUSION:** *TTFields represent a unique technological modality for the effective treatment of glioblastoma multiforme and potentially other solid tumors. Oncology nurses are situated to play important roles as educators and advocates for patients and caregivers on the adherent use and management of this new and evolving treatment technology.*

**IMPLICATIONS FOR NURSING PRACTICE:** *The increasing use of TTFields in cancer treatment draws attention to the expanding role for oncology nurses in the administration of this unique therapy. As an educator and advocate, the oncology nurse guides the cancer patient and caregiver through understanding the mechanism of action, initiation of TTFields treatment, and adjusting to the daily challenges of treatment administration, management of side effects, and optimizing compliance to treatment adherence to maximize treatment outcomes.*

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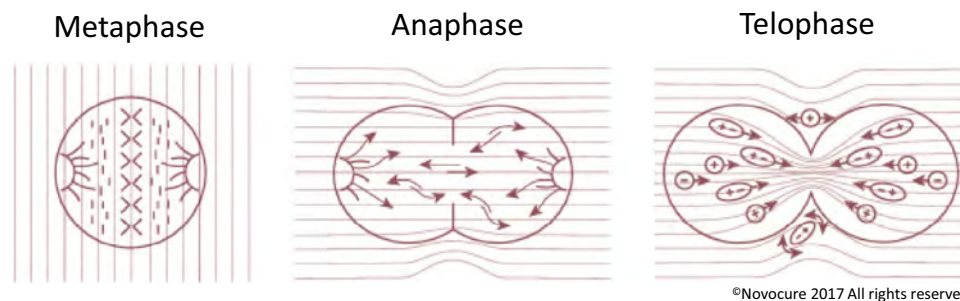
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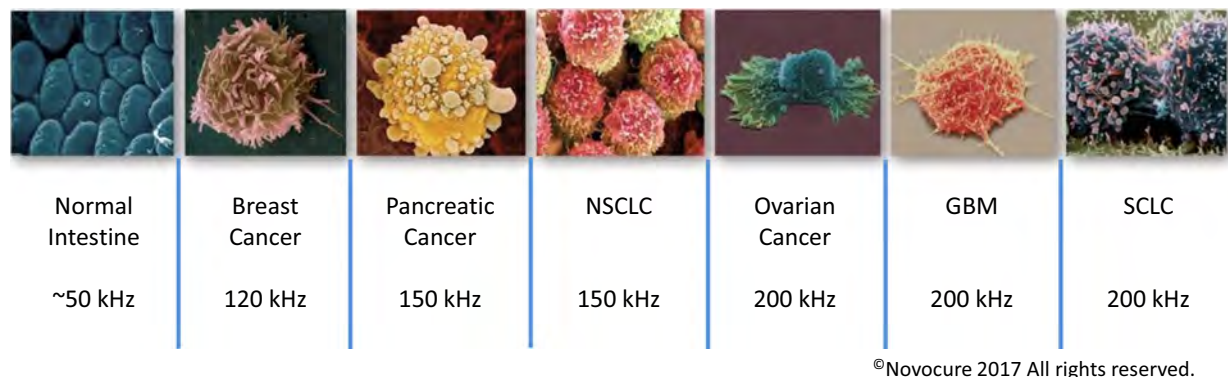
**KEY WORDS:** tumor treating fields, TTFields, glioblastoma, tumor treatment.

**T**umor treating fields (TTFields) are a distinct technological modality for the treatment of solid tumors. TTFields therapy is non-invasive, and the therapeutic effect is achieved through the regional delivery of low-intensity, intermediate frequency-specific (100 to 300 kHz), alternating electric fields to the site of a tumor in the body.<sup>1-3</sup> TTFields are generated between opposing ceramic transducers strategically placed directly on the skin on opposite sides to create alternating electric fields through targeted tumor regions. TTFields act with a high degree of specificity on rapidly replicating cancer cells (Fig. 1), exerting disruptive forces on mitotic spindle formation, resulting in mitotic arrest and cancer cell death. TTFields also exert forces on intracellular organelles and macromolecules during cytokinesis, causing abnormal chromosomal segregation and multinucleation, thus further affecting the replication of daughter cells. Components of

rapidly dividing cancer cells that carry a charge are attracted strongly to the alternating electric fields rather than to the weakly charged intracellular components and forces driving cell division. This leads to incomplete mitosis and apoptosis. Quiescent and non-dividing cells are not affected by TTFields.<sup>4-6</sup> The mechanism of action of TTFields is an area of intense research exploring many concepts, such as the role of immunology, migration, and autophagy.<sup>7,8</sup> The data from these studies demonstrate how TTFields therapy targets cancer cells with electric fields tuned to a specific frequency optimized for suppression of cancer cells in different types of solid tumors. Figure 2 shows micrographic images for cells from different tumor types and the optimal frequency for TTFields to suppress proliferation of cells from specific cancer types. Unlike systemic treatment modalities (eg, chemotherapy), TTFields are only active while the alternating electric fields are applied, underscoring the need for vigilant



**FIGURE 1.** TTFields mechanism of action: TTFields act on rapidly dividing cancer cells by disrupting mitotic spindle assembly during metaphase/anaphase. TTFields also produce nonuniform electric fields within cancer cells affecting intracellular organelles and macromolecules during cytokinesis and causing abnormal chromosomal segregation and multinucleation (telophase) effecting further replication of daughter cells.



**FIGURE 2.** TTFields effects on cancer cells are frequency specific.



adherence to TTFields treatment ( $\geq 18$  hours per day is the recommended duration of treatment of glioblastoma multiforme [GBM] for maximal clinical benefit). TTFields are a wearable, portable medical device that are administered by the patient at home. As a regional targeted therapy, with no systemic half-life, TTFields treatment is not associated with systemic adverse effects and therapy can be stopped immediately should a patient experience any issues with treatment. The use of TTFields is unique among other devices in medicine in that the administration of TTFields with the device has a defined therapeutic effect with beneficial clinical outcomes rather than playing a secondary supportive role.

### CLINICAL DEVELOPMENT OF TTFields FOR GBM

The initial evaluation of TTFields therapy in clinical trials was for the treatment of recurrent GBM in the supratentorial region with TTFields applied at a frequency of 200 kHz. GBM tumors are the most common and aggressive brain tumor in adults with a rapid onset of symptoms and a poor prognosis for survival after primary treatment.<sup>9,10</sup> Preliminary pilot studies in recurrent<sup>1</sup> and newly diagnosed GBM<sup>11</sup> demonstrated the viability of TTFields treatment for GBM with a good tolerability profile. Table 1 summarizes the

**TABLE 1.**  
**Summary of TTFields studies of the treatment of GBM**

Recurrent GBM		
Study	Design	Highlighted outcomes
Kirson et al <sup>1</sup>	Phase I – pilot clinical trial – 10 patients with recurrent GBM	Median time to disease progression was 26.1 weeks and median OS was 62.2 weeks. No device-related serious adverse events were reported over 70 months of cumulative treatment in all patients
Stupp et al <sup>3</sup>	Open-label, phase III trial of chemotherapy-free treatment of NovoTTF (20–24 h/day) vs. active chemotherapy. Patients randomized to TTFields alone (n = 120) or active chemotherapy control (n = 117).	Median survival was 6.6 vs. 6.0 months ( $P = .27$ ), 1-year survival rate was 20% and 20%, PFS rate at 6 months was 21.4% and 15.1% ( $P = .13$ ), respectively, in TTFields and active control patients. The TTFields-related adverse events were mild (14%) to moderate (2%) skin rash beneath the transducer arrays
Newly Diagnosed GBM		
Kirson et al <sup>11</sup>	Pilot clinical trial in recurrent and newly diagnosed GBM patients	In newly diagnosed GBM patients, combining TTFields with temozolomide treatment led to a PFS of 155 weeks and OS of 39 + months
Stupp et al <sup>12</sup>	Interim analysis of an open-label, randomized, phase III trial of TTFields in combination with temozolomide for treatment of glioblastoma after initial treatment with chemoradiation	The interim analysis included 210 patients randomized to TTFields plus temozolomide and 105 randomized to temozolomide alone, and was conducted at a median follow-up of 38 months. Median PFS was 7.1 months in the TTFields plus temozolomide group and 4.0 months in the temozolomide-alone group ( $P = .001$ ). Median OS in the per-protocol population was 20.5 months in the TTFields plus temozolomide group and 15.6 months in the temozolomide-alone group (n = 84) ( $P = .004$ ). TTFields plus temozolomide was not associated with any significant increase in systemic toxic effects compared with temozolomide therapy alone
Stupp et al <sup>13</sup>	Full patient analysis set of open-label, randomized phase III trial of TTFields in combination with temozolomide for treatment of glioblastoma after initial treatment with chemoradiation	A total of 695 patients were randomized; the median PFS is 6.7 months for patients in the TTFields plus temozolomide group vs. 4.0 months in the temozolomide-alone group. Median overall survival from randomization is 20.9 months vs. 16 months for the TTFields plus temozolomide and temozolomide alone, respectively ( $P = .00006$ ).

Abbreviations: GBM, glioblastoma multiforme; OS, overall survival; PFS, progression-free survival.



outcomes of studies on TTFields therapy for the treatment of GBM.

The large EF-11 phase III multicenter clinical trial compared the efficacy and safety of TTFields (200 kHz) alone for the treatment of patients with recurrent GBM to patients treated with standard-of-care chemotherapy.<sup>3</sup> The median survival for the TTFields-treated patients was comparable with the standard of care (6.6 months vs. 6 months) and the 1-year survival rate was 20% for both treatment arms. Progression-free survival (PFS) at 6 months was 21% for TTFields compared with 15% for the standard-of-care treatment group. TTFields therapy was found to be as effective as chemotherapy with fewer side effects. Patients in the TTFields monotherapy treatment arm also reported better quality of life with improved cognitive and emotional functioning.<sup>3</sup> Based on the results of this study, TTFields therapy was approved by the US Food and Drug Administration (FDA) in 2011 for use in adults who have recurrent GBM after receiving chemotherapy and whose disease is refractory to surgical and radiation treatment options.

### **TTFIELDS FOR NEWLY DIAGNOSED GBM**

Preclinical data demonstrated that the combined administration of temozolomide (TMZ) and TTFields to human glioma cells in vitro had an additive cytotoxic effect,<sup>1</sup> suggesting the addition of TTFields to TMZ (the standard maintenance therapy for GBM following surgical resection and chemoradiotherapy) would potentially benefit newly diagnosed GBM patients. Based on this hypothesis, a phase III study was initiated in patients with newly diagnosed GBM in the supratentorial region who had completed concomitant standard-of-care chemoradiotherapy. Patients were randomly assigned (2:1) to receive either TMZ combined with TTFields (200 kHz) or TMZ alone. Based on a pre-specified interim analysis of 315 patients demonstrating positive outcome, the trial was terminated early at recommendation of the independent data and safety monitoring committee and the FDA. Patients in the TMZ-alone arm were allowed to cross over to the TMZ-plus-TTFields group. Two thirds of patients in the combined TTFields and TMZ treatment group continued with TTFields treatment after the first tumor progression.<sup>12</sup> The interim analysis demonstrated that adding TTFields to maintenance TMZ significantly prolonged PFS (7.1 months

vs. 4.0 months (hazard ratio, 0.62 [98.7%CI, 0.43–0.89];  $P = .001$ ) and overall survival (OS; 20.5 months vs. 15.6 months) (hazard ratio, 0.64 [99.4%CI, 0.42–0.98];  $P = .004$ ).<sup>12</sup> Based on these results, the FDA approved TTFields for use in combination with TMZ for the maintenance treatment of adult patients with newly diagnosed GBM. Recent results from the analysis of the 5-year full data set (695 patients) confirm the improvements in PFS and OS seen in the interim analysis.<sup>13</sup> The 2- and 5-year survival rates were 43% versus 31% ( $P = .0008$ ) and 13% versus 5% ( $P = .0037$ ) for TTFields plus TMZ versus the TMZ treatment alone group, respectively. Significant improvement in OS was seen for all patient subgroups. TTFields treatment compliance was the only predictor of outcome, with patients who achieved more than 18 hours/day (monthly average) living significantly longer than patients treated for <18 hours/day.<sup>13</sup> The National Comprehensive Cancer Network guidelines recommend TTFields as a standard treatment category 2A option for newly diagnosed GBM in patients with good functional status.<sup>14</sup>

The objectives of this review are to highlight the technology on which TTFields therapy is based, the impact of its use in the treatment of GBM, as well as discuss the potential evolution of TTFields' technology for the treatment of other tumor types.

### **OPTUNE: PATIENT-OPERATED, HOME-USE TTFIELDS DELIVERY SYSTEM**

The first-generation Optune device (Novocure Inc., Portsmouth, NH; formerly known as the NovoTTF-100A System) was designed for TTFields treatment in the home with minimal impact on activities of daily living. A lighter and more compact second-generation device (NovoTTF200A) was approved for use by the FDA in 2016. [Table 2](#) compares both the first- and second-generation devices. Optune is a CE (Conformité Européenne) marked device approved for use in the European Union, Switzerland, Australia, Israel, and Japan for GBM. The second-generation system takes advantage of improvements in electronic components, circuit boards, and digital signaling technology.

The NovoTTF 200A system<sup>15</sup> is comprised of two primary components: the electric field generator (preset to 200 kHz) and insulated transducer arrays. The device treatment kit includes a plug-in power supply, portable battery, battery rack, battery charger, connecting cables, and carrying case (see



**TABLE 2.**  
First- and second-generation (right) Optune systems for GBM

	First-generation Optune System	Second-generation Optune
<b>Total weight</b> (Device and battery)	6 lbs	2.7 lbs
<b>TTFields generator</b> (The device)	2 lbs	1.5 lbs
<b>Battery Weight</b>	4 lbs	1.2 lbs
<b>Size</b>	Device: 8.3 x 8.3 x 1.75 in Battery: 8.25 x 8.25 x 1.1 in	Device with incorporated battery: 7.1 x 2.3 x 7.6 in
<b>Features</b>	Portability	Easy-grip texture allows for better handling

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photos comparing the first- and second-generation systems in Table 2). Studies in vitro show that the response of cancer cells to TTFIELDS is directionally dependent with higher inhibitory rates of cell replication in cells dividing perpendicular to the electric field direction.<sup>4</sup> Therefore, the placement of the transducer arrays are designed to maximize the clinical effect of TTFIELDS treatment by utilizing two pairs of transducer arrays that are applied directly to the skin to produce two perpendicular electric fields at a specific frequency for the tumor type. Each pair of transducer arrays creates an electric field that is alternating between positive and negative polarity 200,000 times per second (200 kHz) for GBM, and at every second the fields switch between the two pairs of arrays. This is referred to as a duty cycle.

Each transducer array used to treat GBM lesions within the cranium is composed of nine insulated biocompatible ceramic discs connected to a flexible circuit board and in turn to the electric field generator. The field generator is operated at a frequency of 200 kHz when treating GBM. The discs are arranged in a hypoallergenic adhesive bandage to hold them securely in the proper orientation and are attached directly to the shaved bare skin with an intermediary layer of conductive hydrogel.<sup>16</sup> There are reports of patients experiencing warmth

with the transducer arrays in place and the field generator turned on; for safety, each transducer array has eight temperature sensors that will sound an alarm and shut the device off should the temperature of the array exceed 41°C, which is below the temperature for thermal injury.<sup>16</sup> Integrated device system sensors will sound an alarm in the event of operational and safety issues, such as low battery, loose connectors, overheating of the TTFIELDS generator or the transducer arrays, or poor contact between the transducer and skin surface.

The second-generation TTFIELDS device (including the battery) is smaller and lighter with an overall weight of 2.7 lbs (Table 2) and is designed to be carried more comfortably with improved usability for the patient compared with the first-generation device. The second-generation device was made lighter and smaller using unique digital signal generation technology. Additional technical improvements include: a battery indicator that displays power and alerts patients when to change the battery; a light-detecting sensor that automatically dims the device and charger in darker environments; and features “No-Stop Swap” batteries that allows patients to change batteries or power source without turning off delivery of TTFIELDS treatment. Patient feedback regarding the second-generation device highlights the benefits of



quieter operation and portability. Patients experienced fewer alarms and showed greater adherence using the second-generation device that was maintained or improved in most cases compared with the adherence rates observed with the original device.<sup>17</sup>

Adherence with TTFields treatment is critical for clinical benefit. TTFields are a loco-regional therapy, active only while the electric fields are generated between the transducer arrays and distributed to the site of the tumor. Therefore, the clinical effect is only active when the arrays are in place and the TTField generator is on. In a study of post-marketing surveillance, patients with high daily adherence, defined as  $\geq 75\%$  ( $\geq 18$  hours/day) of average daily adherence with TTFields therapy had a significantly longer OS when compared with patients who fell below the 75% therapy duration.<sup>18</sup> A post-hoc analysis of patient data from a pilot study and a phase III trial also demonstrated improved survival with adherence to longer daily duration of therapy ( $\geq 18$  hours/day)<sup>19,20</sup> and treatment compliance was the only predictor for long-term patient survival in the full analysis of the EF-14 trial patient data set.<sup>21</sup>

As monotherapy for recurrent GBM, TTFields in the EF11 study was associated with improvement

in patient-reported assessments of cognitive and social functioning when compared with standard-of-care chemotherapy and symptom scale analysis showed an increase in treatment-associated toxicity directly related to the chemotherapy regimen, such as pain and fatigue that was not reported for patients in the TTFields treatment group,<sup>3,22</sup> suggesting quality of life benefits with TTFields treatment.

In addition to adherence, optimal placement of the transducer arrays may account for improved clinical outcomes. State-of-the-art technological research using modeling and simulations have demonstrated that changing the transducer array placement on the skin to address specific tumor locations results in substantial increases in the induced field intensity within the tumor (Fig. 3), supporting individualized treatment planning for GBM patients.<sup>23</sup> The NovoTAL System is an algorithmic software program validated by a user study group that optimizes transducer array layouts for an individual GBM patient based on head size and tumor location using measurements obtained from magnetic resonance imaging (MRI) data.<sup>24</sup> The algorithm will derive the optimal paired transducer array configuration to deliver the highest intensi-

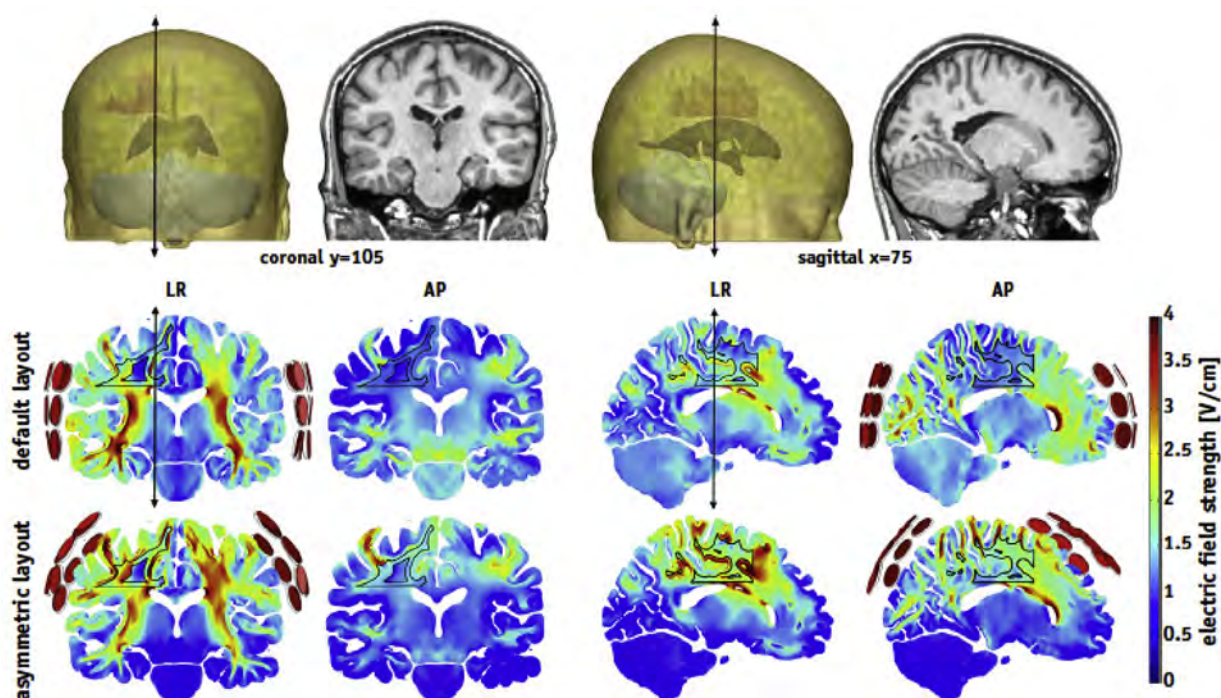


FIGURE 3. Transducer array placement influences TTFields intensity distribution. Simulation studies demonstrate the effect of array placement on electric field intensities across brain tissue. The objectives of such studies are to ensure optimal TTFields intensity at the site of the tumor.<sup>23</sup>



ty of TTFields to the site of a tumor (Fig. 4). The NovoTAL System was approved by the FDA in 2013.<sup>25</sup> The Optune device uses preset treatment levels for frequency (200 kHz for GBM) and a minimal field intensity of 0.7 V/cm across the brain tissue and site of the tumor.<sup>16,26</sup> Follow-up MRI imaging is regularly performed after TTFields therapy is started to track treatment effect and rule out recurrence.<sup>19</sup> In patients with recurrent GBM, 44% of GBM tumors that respond to TTFields treatment initially showed growth before shrinking in size after a median of 4 months with continuous TTFields therapy.<sup>19</sup> A series of case studies presented by Turner et al<sup>27</sup> show evidence for “out-of-field” tumor recurrence potentially because of suboptimal field intensity at the margins of the resected tumor bed. The observations imply that “re-mapping” the transducer array placement based on a change in follow-up MRI, may be an effective strategy to pre-emptively target tumor recurrence.

There are a few important contraindications and warnings associated with using the Optune system for the indicated treatment of either recurrent or newly diagnosed adults with GBM. The device should not be used in patients with active implanted medical devices (ie, deep brain stimulators, vagus nerve stimulators, pacemakers, or defibrillators), skull defects, or bullet fragments.<sup>15</sup> In the United States the FDA requires that the device must be prescribed by a health care provider who has completed certification training provided by Novocure.<sup>15</sup> Optune is classified as durable medical equipment and is typically covered under a patient’s medical benefit with commercial insurance companies. Optune is covered by most commercial insurance companies under published coverage policy or through case-by-case review.

#### PATIENT AND CAREGIVER EDUCATION TO OPTIMIZE TTFIELDS DELIVERY

A GBM patient’s social, cognitive, and physical statuses all play a role in determining whether the patient is a good candidate for TTFields therapy. Patients with physical and cognitive impairment and lacking good daily support are not likely to achieve the recommended adherence goals that are optimal for clinical benefit. Ideally, a patient should have at least one support person who can assist the patient if needed. This is to assist with device alarms, adverse events, and help with removing and

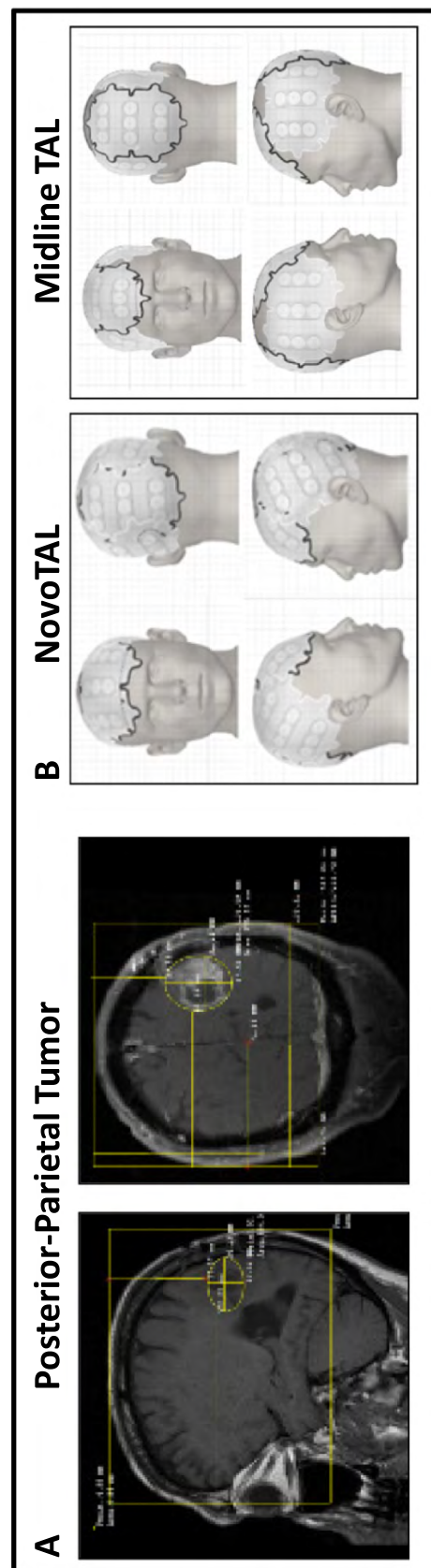


FIGURE 4. NovoTAL treatment planning. (A) Representative NovoTAL treatment planning performed on MRI sagittal and axial T1 post-contrast sequences of a posterior-parietal tumor. (B) Corresponding array layout generated using the NovoTAL System (left) and symmetric midline array configuration for the same tumor (right).<sup>24</sup>



accurately replacing the arrays as part of the normal treatment with TTFields.<sup>28</sup>

Patient and caregiver education are an essential part of TTFields treatment. Each should have a basic understanding of the mechanism of action, the components of the Optune system, how they work, and the importance of meeting treatment adherence goals.<sup>17,29</sup> Patients and caregivers are provided with training in advance of starting therapy with TTFields. This training includes instructions in caring for and maintaining the system components, managing system alarms, and how to prevent and manage skin irritation. Throughout training and follow-up, the importance of adherence to therapy is emphasized.

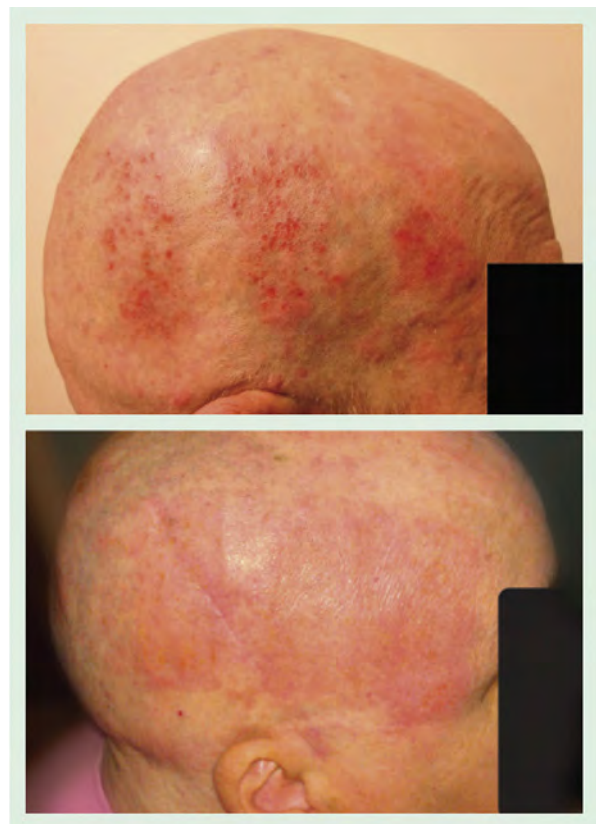
In general, patients are instructed to replace the transducer arrays at least every 4 days,<sup>28</sup> to reshuffle the scalp, and reapply new transducer arrays. Some patients may require more frequent array changing and reshuffling. Used transducers and other system parts are returned for proper disposal. The time period for array replacement depends on individual hair growth, rates of sweating, activity level, and weather.<sup>29</sup> Both the first- and second-generation devices are portable so that patients can participate in activities of daily living with minimal inconvenience (Fig. 5). The redesigned second-generation device is currently used by patients receiving treatment for GBM. The first-generation device is currently used in ongoing investigations in other tumor types delivering therapy at different frequencies. It is also important to note that TTFields therapy poses no danger to anyone in close proximity to the patient. The health care team including nurses supporting the patient and caregiver can help develop strategies to minimize the intru-



**FIGURE 5.** Portability of the Optune device allows patients to participate in activities of daily living. (Photo with permission from the patient.).

sion of TTFields therapy and the device on daily activities. Strategies include selecting wigs and hats if the patient wants to disguise the transducer arrays when out in public. Because restrictive or tightly woven wigs or hats will trap heat and effect device operation, selecting scarves, loosely woven or ventilated wigs appropriately sized for the patient will dissipate heat more effectively while covering the arrays.<sup>29</sup> The cables connecting the power supply and field generator to the transducer array can be arranged under selected layers of clothing to make them less obvious and intrusive.

The device is designed to assist the patient, caregiver, and health care team achieve optimal device-wear time goals. A patient-specific compliance report, compiling daily use times is generated monthly to track the percentage of active TTFields delivered over a 24-hour period. The reports provide tangible evidence for review with the patient and caregiver to help identify issues with adherence so



**FIGURE 6.** Examples of contact dermatitis reactions related to long-term TTFields treatment. Erythema from scalp irritation associated caused by adhesive or hydrogel is shown in the upper panel. The lower panel shows an irritant reaction with erythema associated with the hydrogel between the transducer arrays and the scalp.<sup>16</sup>



that strategies can be adopted to improve treatment duration and potentially improve clinical response.<sup>29</sup> Novocure provides device support specialists trained to assist patients and caregivers with the daily operation of the system.<sup>28</sup> The patient's device support specialist provides comprehensive training and counseling to the patient on the operation of the Optune device and guidance on specific placement of the transducer arrays. The device support specialist also downloads the monthly adherence report, which is provided to the health care team. This is a valuable tool to monitor the patient time on therapy, to reinforce teaching, and to provide coaching on an ongoing basis. The monthly report provides a mechanism to assist with achieving optimal treatment adherence goals.<sup>28</sup> The entire health care team utilizes the data available from the Optune system, along with the full spectrum of clinical data, including MRI imaging, to make the required clinical decisions to optimize treatment outcomes for each patient.

The most common adverse events related to the use of either the first- or second-generation device are scalp irritation and headache.<sup>3,12</sup> These

events are usually mild to moderate in severity and occur below the transducer array and adhesive bandage. Dermatologic adverse events fall into the following categories: irritant contact dermatitis caused by sweat, hydrogel, and/or alcohol; allergic contact dermatitis from a delayed type hypersensitivity reaction to the array adhesive or hydrogel; mechanical erosions from cuts from shaving or removal of the arrays; ulcers caused by inhibited perfusion as a result of the arrays pressing on the skin; and bacterial skin infections.<sup>16</sup> Examples of contact dermatitis reaction-related TTFIELDS treatment are shown in Figure 6. Adequate skin preparation is essential for effective contact between the array transducer and skin, and good scalp hygiene and array placement are critical components of maintaining long-term skin integrity.<sup>28</sup> Effective strategies for preventing and managing skin irritation are summarized in Table 3. Most dermatologic adverse events can be managed with topical treatments and slight adjustment of the transducer arrays to minimize skin irritation.<sup>16</sup> A treatment algorithm for managing dermatologic adverse events is shown in Figure 7.

**TABLE 3.**  
Preventive strategies for dermatological adverse events related to Optune TTFIELDS treatment<sup>16,29</sup>

Category	Guidelines for patient and caregiver
Shaving and preparation of the scalp	<ul style="list-style-type: none"> <li>• An electric shaver is recommended, having a lower risk to cause cuts compared with a razor</li> <li>• Proper hand washing prior to preparing the scalp for array application</li> <li>• Take time shaving the scalp using gentle but firm circular motions</li> <li>• Ensure a close shave before applying the arrays</li> <li>• Cleaning the electric razor after every shave is important to lessen the risk of skin infection</li> <li>• Wash scalp with fragrance-free, mild shampoo (eg, baby shampoo); seborrheic dermatitis shampoo can also be used as it has antibacterial properties (eg, pyrithione zinc 2%, ciclopirox 1%, ketoconazole 2%)</li> <li>• Ensure scalp is completely dry before applying a new set of arrays</li> </ul>
Use of isopropyl (70%) alcohol	<ul style="list-style-type: none"> <li>• Use of first aid antiseptic rubbing alcohol (70% isopropyl alcohol) prior to array application is a necessary step to remove naturally occurring scalp oils, resulting in better adherence of the arrays to the scalp</li> <li>• After shaving and before placing the arrays, wipe the scalp with a gauze or cotton ball soaked in first aid antiseptic rubbing alcohol (70% isopropyl alcohol)</li> <li>• Avoid areas of skin irritation, as the first aid antiseptic rubbing alcohol (70% isopropyl alcohol) may further irritate the skin</li> </ul>
Transducer array exchanges	<ul style="list-style-type: none"> <li>• Change arrays on a regular basis (at least every 3–4 days)</li> <li>• When removing the arrays, avoid “pulling” on the skin; take approximately 60 sec to remove each array</li> <li>• Use of mineral (baby) oil on the edges of the array may make removal of the adhesive tape easier and less irritating to the skin</li> <li>• To remove leftover array adhesive, use gauze or a cotton ball soaked in mineral (baby) oil or pour oil into hands and gently rub scalp in areas of remaining adhesive</li> <li>• Pay close attention to the scalp at each array exchange, and notify the doctor or nurse if there are signs of skin irritation or open areas, to receive information on how to treat them; taking a picture of the affected areas on the scalp and sharing it with the doctor or nurse is advised</li> </ul>



Type of Dermatologic Adverse Event and Recommended Interventions				
Severity	Dermatitis	Erosions	Infections	Ulceration
Preventive	Patient and caregiver education; shifting of transducer arrays; regular (every three to four days) changing of the transducer arrays; close attention to the condition of the skin at time of array exchange and open communication with the healthcare team related to any erythema or irritation; hand washing prior to array exchange to minimize risk of infection; avoiding placement of ceramic discs immediately over screws, wires, or scars; proper ventilation when covering arrays (e.g., ventilated wigs or caps, lightweight scarves)			
<b>For all grades:</b> Advise patients not to place array discs directly over affected area(s) when exchanging arrays. Assess how often the patient is doing an array exchange. Reassess after two weeks (either by healthcare provider or patient self-report). If reaction worsens or does not improve, proceed to guidance for next grade.				
Grade 1	High-potency topical corticosteroid ointments (e.g., clobetasol)	Topical antibiotics (e.g., mupirocin or bacitracin ointment)	Culture, then treat with appropriate topical antibiotic.	Open areas require topical antibiotics.
<b>For grade 1:</b> Reassess after two weeks (either by healthcare provider or patient self-report). If reaction worsens or does not improve, proceed to guidance for next grade.				
Grade 2	High-potency topical corticosteroid ointments and avoidance of direct contact of discs and adhesive tape with affected area(s)	Topical and oral antibiotics and avoidance of direct contact of discs and adhesive tape with affected area(s)	Culture, then treat with appropriate oral antibiotic; avoid direct contact of discs and adhesive tape with affected area(s).	Topical and oral antibiotics and avoidance of direct contact of discs and adhesive tape with affected area(s)
<b>For grade 2:</b> Reassess in two weeks. Consider resuming tumor-treating fields therapy once event has recovered to grade 1.				
Grade 3	Treatment interruption; consider dermatology consultation.	Treatment interruption; consider dermatology consultation.	Obtain skin culture; oral antibiotics; consider treatment interruption until grade 1; consider dermatology consultation.	Treatment interruption; consider dermatology consultation.

FIGURE 7. Treatment algorithm for dermatologic adverse events associated with the use of Optune therapy.<sup>16</sup>

### FUTURE TUMOR TARGETS FOR TTFields

Preclinical studies demonstrate that the optimal anti-proliferative effect of TTFields on isolated cancer cells is dependent on the frequency of the electric fields that is specific to the source of the isolated tumor cells.<sup>4,6,30,31</sup> Therefore, in the clinical setting, TTFields administration is applied at 200 kHz for GBM, representing the frequency with the greatest reduction in glioma cell proliferation<sup>1</sup> and at a frequency of 150 kHz for non-small cell lung cancer cells in vitro.<sup>6,30</sup> TTFields treatment effect is also dose-dependent, where “dose” is equated with the peak-to-peak alternating electric field intensity, which has a minimal threshold value of 1 V/cm. Below this value there is little effect on cancer cell proliferation.<sup>1,4,6,29</sup> Clinical development is currently underway for brain metastases from lung cancers (150 kHz), non-small cell lung

cancer (150 kHz), ovarian cancer (200 kHz), pancreatic cancer (150 kHz), and mesothelioma (150 kHz).<sup>32,33</sup> Details regarding these phase II/III studies are summarized in Table 4. Preclinical studies are ongoing in the following cancer types; breast, cervical, colorectal, gastric, hepatocellular, melanoma, renal, urinary transitional cell and small cell lung cancer.

Radiation therapy (RT) is integral in the standard of care for GBM and other tumor types and targeted immunotherapies are evolving as viable treatment options for a variety of cancers. Preclinical studies suggest that there are synergistic effects for the combination of TTFields with RT and immunotherapies. TTFields administered before RT exposure sensitize glioma cell lines to RT damage and increase antimitotic activity through inhibition of cell survival, cell cycle regulation, and DNA repair activity.<sup>34,35</sup> These results suggest that clin-



**TABLE 4.**  
**Ongoing TTFIELDS clinical trials for cancer<sup>33</sup>**

Tumor type	Study name	Full title	Registration number	TTFIELDS frequency
Brain metastases secondary to NSCLC	COMET	A phase II randomized study of TTFIELD therapy (150 kHz) versus supportive care in non-small cell lung cancer patients with 1–5 brain metastases following optimal standard local treatment	NCT01755624	150 kHz
Ovarian carcinoma	INNOVATE	An open label pilot study of the NovoTTF-100L(O) system (NovoTTF Therapy) (200 kHz) concomitant with weekly paclitaxel for recurrent ovarian carcinoma	NCT02244502	200 kHz
NSCLC	LUNAR	Pivotal, randomized, open-label study of tumor treating fields (TTFIELDS) (150 kHz) in combination with PD-1 inhibitors or docetaxel, for second line treatment of non-small cell lung cancer (NSCLC)	NCT02973789	150 kHz
Brain metastases secondary to NSCLC	METIS	Pivotal, open-label, randomized study of radiosurgery with or without tumor treating fields (TTFIELDS) (150 kHz) for 1–10 brain metastases from non-small cell lung cancer (NSCLC)	NCT02831959	150 kHz
Pancreatic adenocarcinoma	PANOVA	A phase II study of TTFIELDS (150 kHz) concomitant with gemcitabine and TTFIELDS concomitant with gemcitabine plus Nab-paclitaxel for front-line therapy of advanced pancreatic adenocarcinoma	NCT01971281	150 kHz
Mesothelioma	STELLAR	A phase II trial of pemetrexed and cisplatin or carboplatin in combination with TTFIELDS (150 kHz) as first-line treatment in malignant pleural mesothelioma	NCT02397928	150 kHz

ical trials of TTFIELDS in combination with RT should be considered because the combination may improve the clinical benefit of RT. Early evidence suggests that TTFIELDS combined with an immune check point inhibitor (anti-PD-1) augments immunogenic cell death and that combining TTFIELDS with cancer immunotherapies may enhance tumor control.<sup>36</sup> Ongoing research suggests that there are potential complementary or synergistic effects when TTFIELDS are added to chemotherapies or immunotherapies. Localized, regional therapy with TTFIELDS may provide tumor control in combination with therapies having synergistic mechanisms of action without dose-limiting toxicity or compounding any potential adverse effects associated with the systemic treatment. The FDA recently (May 2017) issued a humanitarian use device designation for TTFIELDS for the treatment of pleural mesothelioma, potentially leading to a Humanitarian Device Exemption approval in the United States.

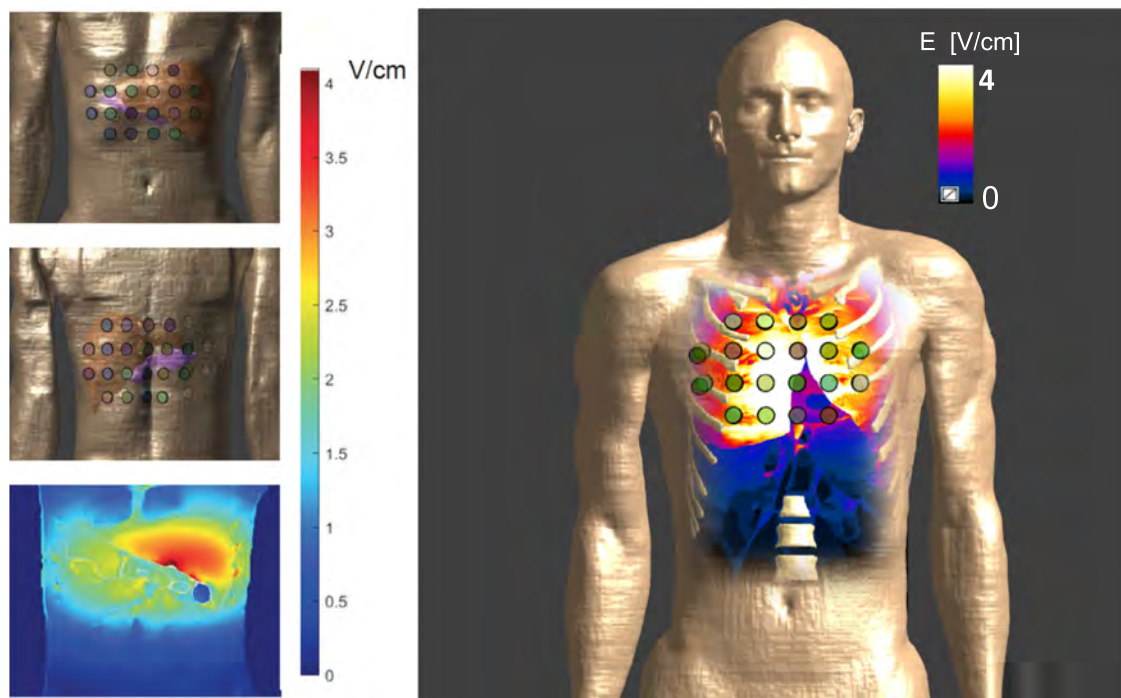
The evolving use of TTFIELDS for tumors in different parts of the body creates technological challenges regarding the design and application of the transducer arrays that deliver therapeutic in-

tensities of TTFIELDS to the site of the tumor and optimize therapeutic outcomes for the patient.<sup>37,38</sup> Digital phantom models (Fig. 8) and simulation analysis demonstrate that effective field intensities can be administered to target tumors in the thorax and abdomen. Typically the number, size, and arrangement of the transducer arrays for tumor treatment in the thorax and abdomen are larger than those used for cranial placement in the treatment of GBM. These parameters along with transducer array placement and arrangement within an array are factors integrated into simulation studies to optimize TTFIELDS delivery to new tumor types and other regions of the body.

#### IMPLICATIONS FOR ONCOLOGY NURSING PRACTICE

The increasing investigational use of TTFIELDS in cancer treatment and the use of the Optune system for the treatment of GBM draw attention to the expanding role for oncology nurses in the





**FIGURE 8.** Calculated electric field intensity in the thorax when TTFields are applied to a male computational phantom model. Simulations demonstrate that optimized array placement can result in delivery of TTFields to treat tumors in the abdominal (right) and thoracic (left) cavities.<sup>37,38</sup>

administration of this emerging therapy. The use of TTFields represents a choice for a different and distinct additional therapeutic modality to consider when treating solid tumors. The best clinical outcomes for TTFields treatment are equated with good daily patient adherence ( $\geq 18$  hours/day). Oncology nurses will play an important role in coaching both the patient and caregiver toward realizing this daily goal. Strategies to maximize adherence and to minimize adverse effects and their severity with prevention and treatment tips are a crucial part of the nursing role in the daily management of TTFields treatment. The importance of compliance should be strongly conveyed to patients by oncology nurses and treating physicians. Most recent reports suggest that patients with compliance over 90% had a median survival of 24.9 months (28.7 months from diagnosis) and a 5-year survival of

29.3%.<sup>39</sup> As an educator, navigator and advocate, the oncology nurse guides the cancer patient and caregiver in decision making, through initiation of TTFields therapy and adjusting to the daily challenges of treatment administration to optimize adherence and treatment outcomes.

### CONCLUSION

TTFields and Optune represent a unique technological modality using a non-invasive at-home device for the effective treatment of GBM and cancerous tumors. Oncology nurses are situated to become important educators and advocates for the patient and caregiver on the adherent use and management of this new and evolving treatment technology.

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# Clinical Cancer Advances 2018: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology

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## A MESSAGE FROM ASCO'S PRESIDENT

I remember when ASCO first conceived of publishing an annual report on the most transformative research occurring in cancer care. Thirteen reports later, the progress we have chronicled is remarkable, and this year is no different. The research featured in ASCO's *Clinical Cancer Advances 2018* report underscores the impressive gains in our understanding of cancer and in our ability to tailor treatments to tumors' genetic makeup.

The ASCO 2018 Advance of the Year, adoptive cell immunotherapy, allows clinicians to genetically reprogram patients' own immune cells to find and attack cancer cells throughout the body. Chimeric antigen receptor (CAR) T-cell therapy—a type of adoptive cell immunotherapy—has led to remarkable results in young patients with acute lymphoblastic leukemia (ALL) and in adults with lymphoma and multiple myeloma. Researchers are also exploring this approach in other types of cancer.

This advance would not be possible without robust federal investment in cancer research. The first clinical trial of CAR T-cell therapy in children with ALL was funded, in part, by grants from the National Cancer Institute (NCI), and researchers at the NCI Center for Cancer Research were the first to report on possible CAR T-cell therapy for multiple myeloma. These discoveries follow decades of prior research on immunology and cancer biology, much of which was supported by federal dollars.

In fact, many advances that are highlighted in the 2018 *Clinical Cancer Advances* report were made possible thanks to our nation's support for biomedical research. Funding from the US National Institutes of Health and the NCI helps researchers pursue critical patient care questions and addresses vital, unmet needs that private industry has little incentive to take on. Federally supported cancer research generates the biomedical innovations that fuel the development and availability of new and improved treatments for patients. We need sustained federal research investment to accelerate the discovery of the next generation of cancer treatments.

Another major trend in this year's report is progress in precision medicine approaches to treat cancer. Although precision medicine offers promise to people with cancer and their families, that promise is only as good as our ability to make these treatments available to all patients. My presidential theme, "Delivering Discoveries: Expanding the Reach of Precision Medicine," focuses on tackling this formidable challenge so that new targeted therapies are accessible to anyone who faces a cancer diagnosis. By improving access to high-quality care, harnessing big data on patient outcomes from across the globe, and pursuing innovative clinical trials, I am optimistic that we will speed the delivery of these most promising treatments to more patients.

Sincerely,

Bruce E. Johnson, FASCO

ASCO President, 2017 to 2018

## EXECUTIVE SUMMARY

Approximately 1.7 million people received a cancer diagnosis in the United States in 2017.<sup>1</sup> Today, more than 15 million Americans, nearly

one in 20, is a survivor of cancer, which means that they have had or are living with cancer.<sup>2</sup> The number of survivors is growing steadily; experts estimate that there will be 26 million by 2040, with 73% 65 years of age or older.<sup>3</sup>

## ASSOCIATED CONTENT



Appendix  
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At the same time, the rate of cancer death has been decreasing, and people are living longer with cancer than ever before. Approximately 64% of US patients diagnosed with cancer in 2005 have lived 10 years or more beyond diagnosis, up from 35% for those diagnosed in 1975.<sup>4</sup>

These trends reflect our and other nations' investments in cancer research and the relentless efforts to advance discovery and care. The volume and pace of cancer research is growing rapidly. For example, the number of medical journal articles with the word "cancer" in the title quadrupled in the last decade, from approximately 28,000 in 2007 to 120,000 in 2017.

Yet more work lies ahead. Because of the aging and growing population, there will be more new patients with cancer every year, both in the United States and worldwide. For every life saved, there are still many people waiting for the next breakthrough for themselves or their loved ones.

This report highlights the most important clinical advances of 2017 and previews where cancer science is headed. New treatments help patients with melanoma and ovarian, lung, bladder, brain, and prostate cancer live longer, and many other new therapies delay cancer worsening or lower the chance of recurrence.

In the span of just 1 year—from November 2016 through October 2017—the US Food and Drug Administration (FDA) approved 31 new therapies for > 16 types of cancer. Among the new approvals are two firsts: an adoptive cell immunotherapy—the ASCO Advance of the Year—and a tumor agnostic therapy, that is, treatment that works against different types of cancers that share a common genetic abnormality.

### **First Adoptive Cell Immunotherapy and Gene Therapy for Cancer**

In August 2017, the FDA approved the first adoptive cell immunotherapy, also known as chimeric antigen receptor (CAR) T-cell therapy, and the first gene therapy for cancer, tisagenlecleucel. This double first approval stems from decades of research on how to train the patient's own immune cells to fight cancer.

Even more important than the historic significance of this achievement is the medical need this unique new therapy is poised to fill. Tisagenlecleucel may be the first treatment to truly turn the tables on recurrent pediatric acute lymphoblastic leukemia (ALL), one of the most common cancers in children. In a clinical trial, cancer in four of five patients went into remission after treatment, which was custom prepared in the laboratory from the patients' own blood cells.

In October 2017, the FDA approved the second CAR T-cell therapy, axicabtagene ciloleucel, to treat adults with certain types of lymphoma. Other CAR T-cell therapies seem promising in clinical trials of people with multiple myeloma. CAR T-cell therapy represents an exciting innovation that has the potential to transform cancer care. It also raises the ongoing issue of cost and reminds us that, as a community, we need to find solutions that will assure that every patient with cancer has access to the care they need. See *Advance of the Year: Adoptive Cell Immunotherapy* for more about these advances.

### **Precision Oncology**

The other historic first among FDA approvals in 2017 marks a milestone in precision oncology. The immune checkpoint

inhibitor pembrolizumab became the first cancer treatment to receive a tumor-agnostic indication. It received accelerated approval to treat any type of solid tumor that has mismatch repair deficiency, a defect that undermines the cell's ability to repair DNA damage. This approval provides patients with a wide range of different cancers an effective way to control the disease.

Another promising treatment, larotrectinib, which homes in on a different, rare genomic abnormality in the tumor known as tropomyosin receptor kinase (*TRK*) gene fusion, also seems to work across tumor types and in both adults and children. Larotrectinib has the potential to become the first tumor-agnostic targeted therapy for cancer.

Meanwhile, fundamental cancer biology research is uncovering new molecular pathways that are being explored as potential therapeutic targets. In 2017 alone, the FDA approved > 13 new targeted medicines for people with leukemia and multiple myeloma, as well as ovarian, breast, and lung cancer.

### **Targeted Agent and Profiling Utilization Registry Study**

In 2017, ASCO's Targeted Agent and Profiling Utilization Registry (TAPUR) Study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02693535) identifier: NCT02693535) continued expanding. As of November 2, 2017, there were > 495 participants enrolled on a study drug at more than 83 sites in 18 states, each offering 17 different targeted therapy options provided by the seven participating pharmaceutical companies.

In addition, the study protocol was revised to lower the age of eligibility for the trial from 18 years to 12 years to extend the opportunity for participation to adolescent patients with advanced cancer in cases in which there is a defined adolescent dose for the study drugs.

The objective for the TAPUR Study is to evaluate molecularly targeted cancer drugs and collect data on clinical outcomes to learn about additional uses of these drugs outside of the indications already approved by the FDA.

The TAPUR Study is registered with a full list of inclusion and exclusion criteria and other information. Prospective patients, researchers, and practices interested in participating can visit the TAPUR website, [TAPUR.org](https://TAPUR.org), or e-mail the TAPUR Study team at [TAPUR@asco.org](mailto:TAPUR@asco.org).

### **Patient-Centered Care**

As life expectancy after a cancer diagnosis continues to improve, there is growing recognition of the need to address patients' emotional and psychosocial needs from the time of diagnosis through treatment and survivorship. *Clinical Cancer Advances 2018* highlights efforts to preserve patient quality of life by avoiding unnecessary treatment or by lowering therapy dose or duration. Furthermore, new tools that engage patients in their own care, such as Web programs for symptom monitoring, psychological support,



and end-of-life planning, are showing benefits for both patients and health care systems.

Finally, we are entering a new era in care in which biomedical research is no longer solely driven by researchers and physicians, but also by patients who are more and more directly engaged in driving progress forward. By donating tissue samples and clinical information, or by helping to design research studies and formulate practice guidelines, patients are providing valuable perspectives and contributing to better care for other patients now and in the future.

### **Federal Support for Cancer Research Is Critical**

Federally funded cancer research has driven many of the major prevention and treatment advances of the past 50 years, and has led to substantial improvements in patient survival and dramatic improvements in quality of life for people with cancer. The National Cancer Institute (NCI) funds studies in areas that private industry has little incentive to address, such as research on cancer prevention, screening, and rare cancers, as well as groundbreaking foundational research.

The US National Institutes for Health (NIH) is the single largest public funder of biomedical research in the world. Federally funded biomedical research helps keep the United States globally competitive by contributing \$65 billion in economic growth, supporting 380,000 jobs, and generating 2.21 dollars in local economic growth for every dollar in NIH funding.<sup>5,6</sup> It is estimated that NIH-funded basic research provides a positive return to public investment of 43%.<sup>7</sup>

Research funded by the NIH also fuels the innovation on which companies depend to bring new treatments to the marketplace, helping make the United States the global leader in developing treatments. Studies show that NIH investments in biomedical research stimulate increased private investment: Every dollar of increase in public clinical research stimulates 2.35 dollars of industry investment at 3 years.<sup>7</sup>

#### **Cancer Research Funding**

More than nine in 10 Americans (91%) believe that the US government should dedicate substantial funding to diagnose, prevent, and treat cancer. Nearly three in four Americans (73%) say the government should spend more to develop cancer treatments and cures, even if it means higher taxes or adding to the deficit (ASCO's National Cancer Opinion Survey, 2017).

Funding from the NIH and other federal agencies supported > 25% of the top advances featured in this report. Among the most notable are studies that have found:

- Prolonged survival with new approaches:
  - A new treatment regimen helps women with recurrent ovarian cancer live longer.
  - A Web-based tool for self-reporting symptoms during chemotherapy helps patients with advanced cancer live longer.

- Longer hormone therapy reduces the risk of breast cancer recurrence.
- Reduced adverse effects with less treatment:
  - Shortening the duration of adjuvant chemotherapy for stage III colorectal cancer is safe and reduces adverse effects.
  - In patients with melanoma, less extensive surgery lowers the risk of lymphedema without compromising survival.
  - Lowering the radiation dose for oropharyngeal cancer reduces health complications without compromising survival.
- Effective strategies to help patients with advanced cancer understand and cope with their prognosis.
- For cancer-related fatigue, exercise and psychological support are more effective than medication.
- New insights on the adverse effects of certain prostate cancer and lung cancer treatments will help inform treatment and survivorship discussions.

In the last year, Congress has made critical investments to improve and accelerate cancer research through supplemental funding for the Cancer Moonshot Initiative and the 21st Century Cures Act. In addition, Congress included a boost in funding for NIH and NCI in fiscal year 2017; however, despite these funding increases, NCI's budget, when adjusted for inflation, remains below prerecession levels<sup>8</sup> (Fig 1).

One manifestation of this reduced budget is that it is more difficult for researchers to secure funding. For example, in 2015, only 16% of new research proposals received funding compared with 27% in 2001.<sup>9</sup> This decline in funding means that it is more difficult for the field to recruit and retain young researchers, which threatens future progress against cancer. Flat funding and budget cuts translate into less innovation, fewer studies launched, fewer patients enrolled in clinical trials, fewer researchers entering the field, and fewer discoveries.

Predictable funding increases are critical to sustain progress against cancer. Dependable and robust funding is essential for planning and conducting multiyear trials that advance new treatments.

#### **A Call to Action to Congress**

Americans are counting on our leaders to invest in biomedical innovation that will deliver the next generation of cancer cures to patients. ASCO urges Congress to give hope to millions of Americans with cancer by continuing to build on its investment in cancer research and providing predictable funding increases to NIH and NCI.

### **About Clinical Cancer Advances**

ASCO develops this annual report, now in its 13th edition, to outline the progress that has been achieved in clinical cancer research and care each year. As a whole, *Clinical Cancer Advances* highlights current trends in the field and previews future directions of cancer research.

The content of this report was developed under the direction of a 20-person editorial board composed of experts in a wide range



# FEDERAL FUNDING IS CRITICAL TO ADVANCING OUR NATION'S CANCER PROGRESS

People with cancer are living better and longer, thanks to our nation's investment in cancer research

▼ **25%**

**DECLINE IN CANCER DEATH RATE**

Since a peak in 1991<sup>1</sup>

**110+**

**NEW CANCER DRUGS OR INDICATIONS APPROVED BY THE FDA SINCE 2006<sup>2</sup>**



**INCREASED 5-YEAR SURVIVAL**

2 out of 3 people with cancer live at least 5 years after diagnosis<sup>1</sup>

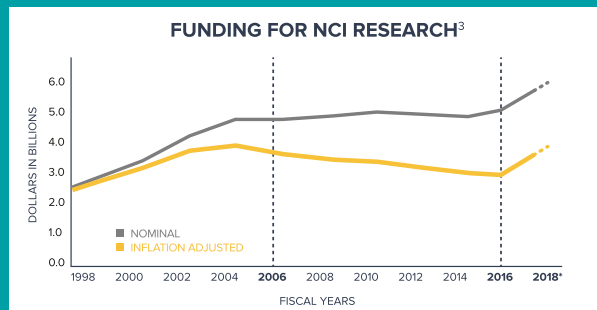
▲ **15.5M**

**CANCER SURVIVORS**

Up from 11.4 million in 2006<sup>1</sup>

NCI's budget, when adjusted for inflation, remains below prerecession levels<sup>3</sup>

**Congress needs to build on its investment**



NIH = National Institutes of Health NCI = National Cancer Institute

<sup>3</sup>Figures do not include additional funding from the 21st Century Cures Act.

Source: National Cancer Institute

**Increased federal funding is urgently needed to accelerate life-saving research and new cancer breakthroughs<sup>4,5</sup>**

**EXPANDED PREVENTION AND DETECTION STRATEGIES**

Boost prevention research and increase testing to identify high-risk patients



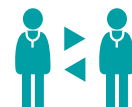
**PRECISION MEDICINE AND IMMUNOTHERAPY RESEARCH**

Support mechanisms to identify, test and validate new predictive biomarkers



**ENHANCED DATA SHARING**

Create a national ecosystem for sharing and analyzing data



**Millions of Americans living with cancer and their loved ones are waiting for new breakthroughs**



**ASCO calls on Congress to build on critical investments by increasing funding to the NIH and NCI.**  
For more information visit [asco.org/nihfunding](https://asco.org/nihfunding).

**ASCO<sup>®</sup>**

Sources: 1. American Cancer Society. Cancer Facts & Figures 2017. Atlanta: American Cancer Society; 2017. 2. U.S. Food and Drug Administration. Approved Drugs – Oncology Drugs. Available at: <http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm>. Accessed on November 9, 2017. 3. National Cancer Institute. NCI Budget and Appropriations. Available at: <https://www.cancer.gov/about-nci/budget>. Accessed on November 9, 2017. 4. The White House. Fact Sheet: Investing in the National Cancer Moonshot. Available at: <https://www.whitehouse.gov/the-press-office/2016/02/01/fact-sheet-investing-national-cancer-moonshot>. Accessed on November 9, 2017. 5. Hayes, Daniel F., MD. "Request for Recommendation of Immediate Actions for the National Cancer Moonshot." Letter to The Vice President. 6 Sept. 2016. MS. Alexandria, VA.

**Fig 1.** Sustained federal funding is needed to accelerate cancer research. FDA, US Food and Drug Administration.



of cancer types, as well as surgical oncology, radiation oncology, cancer prevention and screening, quality of care, health disparities, tumor biology, and developmental therapeutics. The editors reviewed scientific literature that was published in peer-reviewed journals or presented at major medical conferences from October 2016 through September 2017 and selected advances according to formal criteria. Primarily, advances must improve meaningful patient outcomes, such as survival or quality of life, and have a strong scientific impact.

### About ASCO

Founded in 1964, ASCO is committed to making a world of difference in cancer care. As the world's leading organization of its kind, ASCO represents > 40,000 oncology professionals who care for patients living with cancer. Through research, education, and the promotion of the highest-quality patient care, ASCO works to conquer cancer and create a world in which cancer is prevented or cured and every survivor is healthy. ASCO is supported by its affiliate organization, the Conquer Cancer Foundation. Learn more at [www.ASCO.org](http://www.ASCO.org); explore patient education resources at [www.Cancer.Net](http://www.Cancer.Net); and follow us on Facebook, Twitter, LinkedIn, and YouTube.

### Join Us: Tell Your Representatives to Support Cancer Policy Priorities

More than 100 ASCO members from across the country came to the US capitol in September 2017 for ASCO's annual Advocacy Summit, where members urged Congress to support issues critical to improving cancer research and care. During meetings with members of Congress and staff, ASCO members asked Congress to support policies to increase federal research funding, ensure access to chemotherapy services for patients enrolled in Medicare, and improve the affordability of cancer drugs.

ASCO members have an opportunity to make their voices heard throughout the year by engaging with their members of Congress on key issues related to cancer policy. To learn more about participating in ongoing advocacy efforts, visit [asco.org/ACTNetwork](http://asco.org/ACTNetwork).

### The Conquer Cancer Foundation

The Conquer Cancer Foundation was created by the world's foremost cancer physicians of ASCO to seek dramatic advances in the prevention, treatment, and cure of all types of cancer. Toward the vision of a world free from the fear of cancer, Conquer Cancer works to conquer this disease by funding breakthrough cancer research and sharing cutting-edge knowledge with patients and physicians worldwide, and by improving the quality of care and access to care, enhancing the lives of all who are touched by cancer.

Over 34 years, > \$109 million in funding has been provided through Conquer Cancer's Grants and Awards Program to support clinical and translational scientists, at all levels of their careers and working around the globe, to address the full spectrum of oncology, from prevention through survivorship and end-of-life care.

The foundation has given > 1,800 grants and awards in 71 countries. Conquer Cancer grants have helped researchers launch successful careers and make discoveries that benefit patients with cancer.

One of the top patient care advances featured in this report was made possible by funding from Conquer Cancer (see *Patient Engagement Leads to Improved Care*), and several other studies that are highlighted were led by past Conquer Cancer grant recipients who have continued their careers in oncology research.

This report was supported, in part, by funds from Conquer Cancer's Mission Endowment.

### ADVANCE OF THE YEAR: ADOPTIVE CELL IMMUNOTHERAPY

This year, ASCO named adoptive cell immunotherapy as the clinical cancer Advance of the Year. After decades of research, this powerful and decidedly unique way of treating cancer has become available to certain patients with an otherwise incurable blood cancer.

### What Is Adoptive Cell Immunotherapy?

Immune cells navigate the body looking for anything that does not belong—bacteria, viruses, and even cancer cells. They do so by using their molecular feelers, or receptors, to scan for foreign molecules that intruder cells display on their surface. Once an intruder is detected, a class of immune cells, known as cytotoxic T cells, move in to eliminate it.

Unfortunately, cancers have a number of ways to hide from immune cells and avoid their attack. The recently successful immunotherapy approaches aim to remedy this by taking the brakes off the immune system with the use of targeted drugs, known as immune checkpoint inhibitors.

Whereas adoptive cell immunotherapy also boosts the body's immune defenses against cancer, it does so in a completely different way—by genetically re-engineering a patient's own immune T cells. In the late 1980s, an immunologist was the first to experiment with genetically reprogramming T cells, now known as CAR T cells.

CAR T cells are custom made to work against the cancer in each individual patient. To create these cells, researchers collect immune T cells from the patient and insert an artificial gene into the cells. The gene is designed to endow T cells with chimeric antigen receptors that can detect unique molecules on cancer cells after CAR T cells are multiplied in the laboratory and injected back into the patient. In essence, CAR T-cell therapy is both a gene therapy and an immunotherapy.

When the CAR T-cell receptor attaches to a molecule on a cancer cell, it sends a signal to turn on the destruction machinery of the T cell. Unlike traditional cancer treatments, this living therapy needs to be given to the patient only once, because CAR T cells continue to multiply in the patient's body. As a result, the anticancer effects of CAR T cells can persist and even increase over time.



## ***CAR T-Cell Therapy Is Poised to Transform Childhood ALL Treatment***

In 2017, researchers demonstrated that a CAR T-cell therapy known as tisagenlecleucel can eradicate relapsed ALL in children. This represents one of the most remarkable advances in the treatment of childhood cancer in the last decade and could dramatically change treatment paradigms for this disease. Tisagenlecleucel targets a protein, known as CD19, on malignant and normal B cells.

In the United States, ALL will recur in approximately 600 children and young adults per year, despite achieving a response to initial therapy. After a relapse, ALL is difficult to treat, and survival is usually measured in weeks to months. Remission rates with current standard therapies in prior clinical trials have been only 20% with chemotherapy and 33% with targeted therapy.<sup>10,11</sup>

In a clinical trial of children and young adults with relapsed or refractory ALL, cancer went into remission within 3 months of receiving tisagenlecleucel in 52 (82%) of 63 patients, and 75% of patients remained relapse free at 6 months.<sup>12,13</sup> On the basis of these findings, the FDA approved tisagenlecleucel for the treatment of children and young adults with B-cell ALL in August 2017.<sup>14</sup>

This global clinical trial confirmed the high efficacy that was demonstrated in prior, single-institution trials; however, the rate of immune-related adverse effects was high with tisagenlecleucel. Nearly 50% of patients experienced severe cytokine release syndrome (CRS), a complication during which CAR T cells produce a storm of inflammatory molecules. CRS can cause prolonged fever, low blood pressure, difficulty breathing, and problems with multiple organs. If severe, CRS may require intensive medical care, such as the use of a ventilator or medications known as pressors to increase blood pressure, and seizure medication. Although CRS can be serious and even life threatening, doctors now have an effective medicine (tocilizumab) with which to curb and, in most cases, fully reverse the symptoms.

In addition, neurologic complications occurred in 15% of patients in the study. A broad range of neurologic problems, including word recall issues, difficulty speaking, reduction of alertness, delirium, hallucinations, seizures, and coma, have been reported in prior clinical trials with CAR T-cell therapies. In most patients, such symptoms resolved on their own within a few days without long-term consequences, but several deaths have occurred, with severe neurologic complications in other CAR T-cell trials. In this ALL trial, there were no deaths related to either CRS or neurologic complications.

The global ALL trial also helped to prove that patient access to this novel treatment could be broadened. It was the first time CAR T cells were produced from patient blood cells in an industrial manufacturing facility and distributed to patients via a global supply chain that included 25 centers in the United States, Canada, Europe, Australia, and Japan. Until then, the production of CAR T cells was limited to few academic laboratories, without the ability to ship the cell product to patients around the world.

## ***CAR T-Cell Therapy Is Effective Against Hard-to-Treat Lymphoma in Adults***

CAR T cells that target CD19 have also been proven to be promising against another hard-to-treat cancer, diffuse large B-cell

lymphoma (DLBCL), which is the most common type of non-Hodgkin lymphoma.

In a multicenter clinical trial of patients with DLBCL that worsened after at least two prior therapies, the cancer responded to tisagenlecleucel in 59% of 51 patients and went into remission in 43% of patients.<sup>15</sup> At 6 months, 79% of patients had not had a recurrence of lymphoma. Severe CRS occurred in 25% of patients, and neurologic complications in 13%.

In a different clinical trial, patients with relapsed or refractory DLBCL, refractory primary mediastinal B-cell lymphoma, or transformed follicular lymphoma, received another CAR T-cell product called axicabtagene ciloleucel that also targets CD19.<sup>16</sup> Among the first 92 patients who were treated, the response rate was 82%, with complete remissions occurring in 54% of patients. At a median follow-up of 8.7 months, 39% of patients were still in complete remission. Severe CRS occurred in 13% of patients; neurologic adverse effects occurred in 28% of patients. In late 2017, the FDA approved axicabtagene ciloleucel to treat adults with DLBCL that has not responded to, or has recurred, after at least two prior therapies.<sup>17</sup>

## ***CAR T-Cell Therapy Sends Multiple Myeloma Into Remission***

The studies described above all included CAR T cells that were targeted to the B-cell biomarker CD19. A different type of CAR T-cell therapy that targets a biomarker known as B-cell maturation antigen seems to be effective against multiple myeloma. Despite recent advances in treatment, multiple myeloma—a cancer of plasma cells that make antibodies to fight infections—remains an incurable disease, with only approximately one half of patients living 5 years after diagnosis.

In an early clinical trial, the cancer responded to B-cell maturation antigen CAR T cells in 33 (94%) of 35 patients, and went into complete remission in 14 patients<sup>18</sup> (updated data presented at the 2017 ASCO Annual Meeting in Chicago, IL). Only two patients experienced severe CRS, and none experienced neurologic complications from CAR T-cell therapy.

## **ADVANCES IN CANCER PREVENTION**

Cancer prevention efforts, including cancer screening, vaccination, tobacco control, healthy eating, and physical activity, remain key to reducing the effect of cancer and improving outcomes across communities worldwide. In fact, researchers estimate that 50% of cancer cases and deaths in the United States could be prevented if people adopted simple healthy lifestyle choices that include avoiding smoking and alcohol, maintaining a healthy weight, and exercising regularly.<sup>19</sup>

The top three causes of cancer-related death in low-resource countries—liver cancer, stomach cancer, and cervical cancer—are largely preventable through screening or vaccination. In higher-resource countries, two leading causes of cancer-related deaths—lung and colorectal cancer—can be lowered through lifestyle changes, such as increased physical activity and avoidance of alcohol, tobacco, and processed meat. The same healthy habits can help prevent dozens of other cancers. Emerging research suggests that



human papillomavirus (HPV) vaccination, mainly used for the prevention of cervical cancer, may also help reduce head and neck cancers by lowering oral HPV infections.<sup>20</sup> Finally, safe sun exposure practices and avoidance of indoor tanning can substantially lower the risk for melanoma.

### Preventive Actions to Lower Cancer Risk

Although most Americans (66%) do not smoke, less than half take other important preventive actions to lower their risk of cancer:

- Use sunblock or limit sun exposure without sunblock (48%)
- Exercise regularly (48%)
- Maintain a healthy body weight (41%)
- Limit alcohol consumption (38%) (ASCO's National Cancer Opinion Survey, 2017).

### Avoidable Cancer Risk Factors: E-Cigarettes May Spur Increases in Smoking

In 2017, two federally funded studies provided the clearest estimates of how e-cigarette use may lead to a future habit of smoking cancer-causing traditional tobacco cigarettes. The first study found that people 14 to 30 years of age who used e-cigarettes were 3.6 times more likely to begin smoking traditional cigarettes than those who never used e-cigarettes (this study was funded, in part, by grants from the NCI, the FDA and the National Institute on Drug Abuse).<sup>21</sup> These findings indicate that e-cigarettes are not merely a substitute for traditional cigarettes, but are also a strong risk factor for future smoking. In fact, experts caution that e-cigarette use may lead to an upsurge in smoking prevalence in the long term.

Another study found that, among US teenagers 12 to 17 years of age, the rate of e-cigarette use is already approaching the rate of tobacco cigarette use; 3.1% smoked e-cigarettes compared with 4.6% who smoked tobacco cigarettes in the last 30 days (this study was funded, in part, by grants from the National Institute on Drug Abuse, NIH, and the FDA).<sup>22</sup> However, among adults, e-cigarette use still lags far behind tobacco cigarette use (6.7% v 22.5%). In addition, among those who used more than one tobacco product, 15% of teenagers and 23% of adults used both e-cigarettes and traditional cigarettes.

There is clear evidence that e-cigarettes, smokeless tobacco, and water pipes may cause serious health problems, including cancer. Because of these potential health risks, the FDA began regulating these products, along with other tobacco products, on August 8, 2016. The US Centers for Disease Control and Prevention calls on the public, including parents, health care providers, and teachers, to discourage e-cigarette use among youth. ASCO's [Cancer.Net](#) provides information on the risks of e-cigarettes and smokeless tobacco.

### Cancer Spending

Almost one half (49%) of Americans believe that the government should spend more money on cancer prevention, and 54% think the government should spend more to help Americans afford cancer screenings and care (ASCO's National Cancer Opinion Survey, 2017).

### Avoidable Cancer Risk Factors: Indoor Tanning

UV radiation exposure from indoor tanning is a cause of malignant melanoma. Characterizing the risk of melanoma associated with use of UV radiation-emitting devices is critical for developing policies that reduce the use of such devices, but much of the evidence on this topic has come from case-control studies. In the past year, a large, prospective study was reported that adds new weight to such policy efforts, finding that the risk for melanoma rose with an increasing number of indoor tanning sessions.<sup>23</sup> Compared with those who never used indoor tanning, women who started indoor tanning before 30 years of age had a 30% higher risk for melanoma, which suggests that the harmful effects of indoor tanning are greater at a younger age. For more information on risk factors for melanoma, visit [Cancer.Net](#).

### ASCO Issues Statement on Alcohol as It Relates to Cancer Prevention

In 2017, ASCO issued a statement on alcohol and cancer aimed at drawing attention to alcohol consumption as a contributing factor to the overall cancer burden.<sup>24</sup> ASCO cites between 5% and 6% of new cancer cases and deaths globally as being directly attributable to alcohol. This is particularly concerning as 70% of Americans do not recognize drinking alcohol as a risk factor for cancer, according to the National Cancer Opinion Survey, conducted by ASCO in 2017.

Because drinking alcoholic beverages is a potentially modifiable risk factor for cancer, it can be targeted with preventive interventions at both the policy and individual levels to reduce the incidence of cancer. The evidence-based policy recommendations to reduce excessive alcohol consumption listed in the statement, which was published in *Journal of Clinical Oncology*, are:

- Provide alcohol screening and brief interventions in clinical settings;
- Lower the number of alcohol retailers per capita;
- Increase alcohol taxes and prices;
- Maintain limits on days and hours of sale;
- Enhance enforcement of laws that prohibit sales to minors;
- Restrict youth exposure to advertising of alcoholic beverages;
- Resist additional privatization of retail alcohol sales in communities with current government control;
- Include alcohol control strategies in comprehensive cancer control plans; and
- Support efforts to eliminate the use of "pinkwashing" to market alcoholic beverages (ie, discourage alcoholic beverage companies from exploiting the color pink or pink ribbons to show a commitment to finding a cure for breast cancer) given



the evidence that alcohol consumption is linked to an increased risk of breast cancer.

In addition, not only does excessive alcohol consumption cause cancer, it also can delay or negatively affect cancer treatment. Oncologists are uniquely positioned to identify strategies to help their patients reduce alcohol use; address racial, ethnic, gender, and sexual orientation disparities that may place these populations at increased risk of cancer; and serve as community advisors and leaders to raise awareness of alcohol as a cancer risk behavior.

The link between alcohol use and cancer treatment is one of the most-needed areas for future research in the oncology community, particularly in studying the effect of alcohol consumption while undergoing cancer treatment, including chemotherapy, radiation, and surgery. Other underexplored research areas include the effect of alcohol consumption on postoperative morbidity and targeted therapies, such as immunotherapy and radiation. By increasing the community's knowledge of the ways in which alcohol affects cancer and cancer treatments, oncologists and researchers may have a better understanding of its role in disease progression and therapeutic responsiveness and toxicity.

#### ADVANCES IN CANCER TREATMENT

This year, > 14 million people worldwide will learn they have cancer. According to the latest global statistics, nearly 9 million people a year lose their lives to cancer. That equates to approximately 22,000 cancer deaths per day.<sup>25</sup> The global cancer burden is expected to grow in the future, reaching 21 million patients with cancer and 13 million deaths per year by 2030, as the world's population expands and ages. These sobering statistics underscore the urgency of finding better treatments for patients today and in the future.

The number of new FDA approvals in oncology in recent months is reflective of the scientific fervor and innovation underway to fill this need. From November 2016 through October 2017, the FDA approved a record 18 new cancer therapies and 13 new uses of cancer therapies (Table 1). By comparison, in the same timeframe in the previous year, there were eight new cancer therapies and 13 new uses approved, and a similar number in 2015. Most, if not all, of these new and expanded uses are associated with an improvement in patient survival and/or quality of life.

Also historic, 2017 marked the first approval of a tumor-agnostic therapy and the first adoptive T-cell and gene therapy for cancer, demonstrating that the breakthrough therapy designation and other new approaches in oncology drug development have allowed for a more efficient review and approval process. Research results on other immunotherapies and targeted therapies released in 2017 have changed the treatment paradigms for lung, prostate, and bladder cancer.

#### ***Emergence of Tissue-Agnostic Therapies: Treating Patients on the Basis of the Tumor's Genetics, Rather Than Its Location***

Historically, cancer therapies have been approved for use on the basis of the tumor's location in the body and stage of cancer.

Last year marked a milestone in the history of precision cancer medicine and cancer drug approvals: In May, the FDA approved the first tissue-agnostic treatment, which means that it was approved for use solely on the basis of the genetic make-up of a person's cancer, rather than the type of cancer or its location in the body.<sup>26</sup> Pembrolizumab was approved for the treatment of adults or children with advanced solid tumors that harbor specific genomic changes—mismatch repair (MMR) deficiency or high microsatellite instability (MSI-H).

FDA approval was based on findings from 149 patients with MMR-deficient or MSI-H solid tumors—90 had colorectal cancer and 59 had one of 14 other types of cancer—who were enrolled in five clinical trials. Tumors shrank in 40% of patients, and in 78% of those patients, tumor response lasted  $\geq 6$  months. In one of the studies that included patients with 12 different types of cancer, 21% of patients experienced a complete remission of cancer (this study was funded, in part, by grants from the NIH).<sup>27</sup>

Cells with MMR deficiency have a lower ability to repair damage to their genetic material or DNA and, as a result, accumulate a high number of mutations and make many abnormal proteins. Recent research has shown that programmed death-1/programmed death ligand-1 immune checkpoint inhibitors, which work by unleashing the immune response to cancer, are particularly effective against tumors with MMR deficiency. The reason for this is thought to be a stronger immune response to tumors with more abnormal proteins that the immune system recognizes as foreign.

With this approval, subsets of patients with various types of cancer that are otherwise resistant to treatment gained a highly effective treatment option for controlling the disease, potentially long term. Testing for MMR deficiency or MSI-H will become part of routine diagnostic workup for many patients with solid tumors.

In 2017, researchers presented the early findings from a study of another treatment that seems to work well across many different types of adult and pediatric cancers. The treatment, called larotrectinib, selectively targets a rare genomic abnormality, the tropomyosin receptor kinase (*TRK*) gene fusion.

It is estimated that this abnormality occurs in approximately 0.5% to 1% of many common cancers. In addition, > 90% of certain rare cancers, such as salivary gland cancer, pediatric breast cancer, and infantile fibrosarcoma, have *TRK* fusions.

Of the first 50 adults and children with 17 different cancer types who received larotrectinib in clinical trials, treatment response rate was nearly 80%.<sup>28</sup> Responses to larotrectinib have been long lasting, with 79% ongoing at 12 months after starting treatment. The most common adverse effects were fatigue and mild dizziness, which were expected, as the normal *TRK* protein has a role in controlling balance. No patients needed to stop treatment as a result of adverse effects.

In another clinical trial that enrolled 12 young children with different cancers that harbored *TRK* fusions (infantile fibrosarcoma, other sarcomas, and papillary thyroid cancer) the response rate to larotrectinib was 92%, and responses were also durable. At 6 months, the cancer had worsened in only one patient.<sup>29</sup>

These trials that show strong tumor responses in tumors with *TRK* fusions, regardless of histology, represent a major development in the field. These findings pave the way for a new class of



**Table 1.** FDA Approvals of Cancer Therapies From November 1, 2016, to October 31, 2017

Drug	Indication	Approval Date
<b>New approval</b>		
Rucaparib (Rubraca; Clovis Oncology, Boulder, CO)	For treatment of patients with deleterious BRCA mutation (germline and/or somatic)-associated advanced ovarian cancer who have been treated with two or more chemotherapies.	December 2016
Avelumab (Bavencio; EMD Serono, Darmstadt, Germany)	For the treatment of patients $\geq 12$ years of age with metastatic Merkel cell carcinoma. Avelumab is a PD-L1-blocking human immunoglobulin G1 $\lambda$ monoclonal antibody. This is the first FDA-approved product to treat this type of cancer.	March 2017
Niraparib (Zejula; Tesaro, Waltham, MA)	Maintenance treatment for adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.	March 2017
Ribociclib (Kisqali; Novartis, Basel, Switzerland)	In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer.	March 2017
Brigatinib (Alunbrig; Takeda, Osaka, Japan)	For treatment of patients with metastatic anaplastic lymphoma kinase-positive NSCLC who experienced disease progression on or who are intolerant to crizotinib.	April 2017
Midostaurin (Rydapt; Novartis)	For treatment of adult patients with newly diagnosed AML who are FLT3 mutation-positive, as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.	April 2017
Durvalumab (Imfinzi; AstraZeneca, London, United Kingdom)	For treatment of patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or who experience disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.	May 2017
Rituximab and hyaluronidase human (Rituxan Hycela; Genentech, South San Francisco, CA)	For adult patients with follicular lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia.	June 2017
Neratinib (Nerlynx; Puma Biotechnology, Los Angeles, CA)	For extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy.	July 2017
Daunorubicin and cytarabine (Vyxeos; Jazz Pharmaceuticals, Palo Alto, CA)	For treatment of adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes, two types of AML that have a poor prognosis.	August 2017
Enasidenib (Idhifa; Celgene, San Francisco, CA)	For treatment of adult patients with relapsed or refractory AML with an isocitrate dehydrogenase-2 mutation as detected by an FDA-approved test.	August 2017
Inotuzumab ozogamicin (Besponsa; Wyeth, Madison, NJ)	For treatment of adults with relapsed or refractory B-cell precursor ALL.	August 2017
Tisagenlecleucel (Kymriah; Novartis)	For treatment of patients $\leq 25$ years of age with B-cell precursor ALL that is refractory or in second or later relapse.	August 2017
Abemaciclib (Verzenio; Eli Lilly, Indianapolis, IN)	In combination with fulvestrant for women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression after endocrine therapy.	September 2017
Bevacizumab-awwb (Mvasi; Amgen, South San Francisco, CA)	Approved as a biosimilar to bevacizumab (Avastin), bevacizumab-awwb is the first biosimilar approved in the United States for the treatment of cancer.	September 2017
Copanlisib (Aliqopa; Bayer HealthCare, Berlin, Germany)	For treatment of adult patients with relapsed follicular lymphoma who have received at least two prior systemic therapies.	September 2017
Gemtuzumab ozogamicin (Mylotarg; Pfizer, New York, NY)	Newly diagnosed CD33-positive AML in adults and for treatment of relapsed or refractory CD33-positive AML in adults and pediatric patients $\geq 2$ years of age. May be used in combination with daunorubicin and cytarabine for adults with newly diagnosed AML or as a stand-alone treatment of certain adult and pediatric patients.	September 2017
Axicabtagene ciloleucel (Yescarta; Kite Pharma, Los Angeles, CA)	For treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy.	October 2017
<b>New use</b>		
Daratumumab (Darzalex; Janssen, Beerse, Belgium)	In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.	November 2016
Nivolumab (Opdivo; Bristol-Meyers Squibb, New York, NY)	Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy.	November 2016
Lenalidomide (Revlimid; Celgene)	Maintenance therapy for patients with multiple myeloma after autologous stem-cell transplantation.	February 2017
Nivolumab (Opdivo)	For treatment of patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or experience disease progression within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing chemotherapy.	February 2017
Osimertinib (Tagrisso; AstraZeneca)	For treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, who experienced disease progression on or after EGFR tyrosine kinase inhibitor therapy.	March 2017

(continued on following page)



**Table 1.** FDA Approvals of Cancer Therapies From November 1, 2016, to October 31, 2017 (continued)

Drug	Indication	Approval Date
Palbociclib (Ibrance; Pfizer)	HR-positive, HER2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women.	March 2017
Pembrolizumab (Keytruda; Merck & Co, Kenilworth, NJ)	For treatment of adult and pediatric patients with refractory classic Hodgkin lymphoma or those who have experienced relapse after three or more prior lines of therapy.	March 2017
Regorafenib (Stivarga; Bayer HealthCare Pharmaceuticals)	For treatment of patients with HCC who have been previously treated with sorafenib.	April 2017
Avelumab (Bavencio)	For patients with locally advanced or metastatic urothelial carcinoma who experienced disease progression during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.	May 2017
Pembrolizumab (Keytruda)	In combination with pemetrexed and carboplatin for treatment of patients with previously untreated metastatic nonsquamous NSCLC.	May 2017
Pembrolizumab (Keytruda)	For patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.	May 2017
Nivolumab (Opdivo)	For treatment of HCC in patients who have been previously treated with sorafenib.	September 2017
Pembrolizumab (Keytruda)	For patients with recurrent locally advanced or metastatic, gastric, or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 as determined by an FDA-approved test.	September 2017

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NSCLC, non-small-cell lung cancer; PD-L1, programmed death-ligand 1.

drugs for rare tumors and define a new era in oncology. Equally important, they set a new milestone in precision medicine for pediatric oncology, for which it is just starting to be applied.

### A Policy Focus: FDA's New Plan to Increase Medical Innovation

The FDA has launched a new Medical Innovation Development Plan designed to facilitate the development of innovative drugs by updating FDA's regulatory tools and policies. FDA intends to use the new plan to streamline the path to market for targeted therapies and other novel drugs to encourage innovation in therapies. In particular, the plan will focus on facilitating the approval of tumor-agnostic therapies—medicines that work comparatively well in many different types of cancer. As part of the plan, FDA will develop guidance on strategies to improve the efficiency of clinical trials, including adaptive trial designs.

### New Treatments Slow Advanced Lung Cancer Growth

Lung cancer is among the most common types of cancer and the leading cause of cancer death in men and women worldwide. Last year, an estimated 156,000 people died of this disease in the United States.<sup>30</sup>

The good news is that these grim statistics have been steadily improving. After decades of increases, rates of lung cancer deaths began to decline in the early 1990s and have been falling, on average, 2.5% each year between 2005 and 2014. The 5-year

survival rate increased from only 11% in 1975 to 18% in the most recent time period measured (2007 to 2013).<sup>30</sup> For more information about lung cancer, visit [Cancer.Net](#).

This progress is directly tied to changes in therapy that have occurred during the past two decades, with the development of new therapies that not only work better, but that often also have fewer adverse effects than standard chemotherapy, radiation, and surgery.

In 2017, two new regimens were introduced for the initial treatment of the most advanced form of non-small-cell lung cancer (NSCLC)—a targeted medicine, alectinib, and an immune checkpoint inhibitor, pembrolizumab, combined with chemotherapy. For patients with earlier-stage disease, a clinical trial demonstrated that administering a new immune checkpoint inhibitor, durvalumab, after standard chemotherapy and radiation dramatically slowed cancer growth.

*New targeted medicine works better than chemotherapy and with fewer adverse effects.* Up to 7% of NSCLCs have a genetic change known as anaplastic lymphoma kinase (ALK) rearrangement that results in an abnormal ALK protein that causes cells to grow and spread. The first medicine that targets ALK, crizotinib, was approved by the FDA in 2011, and more potent medicines have been introduced since that time. In 2017, two clinical trials showed that one new ALK medicine, alectinib, is more effective than crizotinib for patients with previously untreated NSCLC, and also causes fewer adverse effects.<sup>32,33</sup> In the larger of the two trials, during a median follow-up of 18 months, 41% of patients who received alectinib had their cancer worsen, or died, compared with 68% of those who received crizotinib.<sup>33</sup> Alectinib was also better at curbing the growth of cancer that had spread to the brain; only 12% of patients had worsening brain metastases compared with 45% of those who received crizotinib.



## Changing Paradigms in Lung Cancer Treatment

The first paradigm shift occurred in the mid-1990s with research that demonstrated that giving chemotherapy after surgery, known as adjuvant therapy, helps patients live longer, and that combining chemotherapy with radiation therapy can additionally improve the outlook for some patients with lung cancer. Several new chemotherapies were introduced, such as paclitaxel, docetaxel, gemcitabine, and pemetrexed.

The second paradigm shift in the treatment of advanced lung cancer occurred in 2004, when scientists discovered the association between certain mutations in the epidermal growth factor receptor (EGFR) and response to EGFR-targeted drugs, such as gefitinib. EGFR is a protein that helps cancer cells grow and is mutated in 25% of lung cancers. In the ensuing years, several EGFR-targeted drugs were developed (erlotinib, afatinib, and osimertinib) as well as treatments that target less common genetic alterations (*BRAF* gene mutations [dabrafenib plus trametinib] and *ALK* gene rearrangements [crizotinib, ceritinib, and alectinib]).

Finally, the introduction of immunotherapy in 2015 marks the third paradigm shift in the treatment of lung cancer. Immune checkpoint inhibitors, pembrolizumab and nivolumab, were first approved for the treatment of advanced NSCLC that worsens during or after standard chemotherapy, and atezolizumab was approved in 2016. That same year, the FDA approved the first use of immunotherapy for previously untreated advanced NSCLC, pembrolizumab. Currently, immunotherapy is also being studied in earlier stages of disease. In a clinical trial of patients with locally advanced, stage III NSCLC, the checkpoint inhibitor durvalumab delayed disease worsening by nearly 1 year. The ongoing ALCHEMIST immunotherapy trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02595944) identifier: NCT02595944) explores whether giving nivolumab after standard treatment of early-stage lung cancer can reduce recurrences and help patients live longer.

Reflecting on these developments, ASCO's clinical practice guideline for advanced NSCLC was revised in 2017 to add immunotherapy as a standard treatment approach for either first-line or second-line settings.<sup>31</sup>

*Role of immunotherapy continues to expand, slowing advanced cancer growth.* In 2017, the FDA granted accelerated approval to pembrolizumab combined with standard chemotherapy (carboplatin and pemetrexed) as an initial treatment of metastatic NSCLC.<sup>34</sup> The approval was based on an early clinical trial that found that the chance of cancer worsening was cut nearly in half by adding pembrolizumab to chemotherapy. The median time until cancer worsening was 13 months with pembrolizumab and chemotherapy versus 9 months with chemotherapy alone; however, the incidence of serious treatment-related adverse effects was

higher with combined modality treatment (41%) than chemotherapy alone (28%). An international phase III clinical trial is underway to confirm these findings ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02578680) identifier: NCT02578680).

A newer immune checkpoint inhibitor, durvalumab, also seems to have a role in lung cancer treatment. These findings mark the first advance in years for the treatment of stage III, locally advanced NSCLC. This type of cancer accounts for approximately one third of all NSCLCs. The standard treatment of patients with tumors that cannot be surgically removed is chemotherapy with radiation, or chemoradiotherapy. Despite this treatment, cancer quickly worsens, and only 15% of patients are alive 5 years after diagnosis.

In this trial, patients whose cancer did not worsen after chemoradiotherapy were randomly assigned to receive durvalumab or placebo.<sup>35</sup> The median time until cancer worsening was 16.8 months with durvalumab and 5.6 months with placebo, and the median time until patients died or the cancer spread to distant parts of the body was 23.2 months versus 14.6 months, respectively.

## Continued Research on Immune Checkpoint Inhibitors

Uses for immune checkpoint inhibitors—treatments that help unleash the body's immune response to cancer—continue to expand to more cancer types, which has affirmed the role of this strategy, and particularly agents that target the programmed death-1/programmed death ligand-1 checkpoint in cancer treatment. Key recent studies in this area are listed in [Table 2](#).

## Immunotherapy Changes the Treatment Paradigm for Bladder Cancer

Bladder cancer is another type of cancer for which immunotherapy has transformed the outlook for patients. The most common type of bladder cancer, urothelial cancer, is difficult to treat at advanced stages. With standard chemotherapy, only 5% of patients are alive 5 years after diagnosis. For more information about bladder cancer, visit [Cancer.Net](https://www.cancer.net).

After 30 years of limited progress, the outlook for these patients is now improving with the arrival of a series of immunotherapies ([Table 3](#)). For some patients, immunotherapy has opened a treatment option where none previously existed. For others, it offers a chance to live longer with fewer treatment-related adverse effects.

In May 2016, atezolizumab became the first immune checkpoint inhibitor to receive FDA approval for the treatment of advanced bladder cancer.<sup>49</sup> In 2017, the FDA approved four other immune checkpoint inhibitors for patients with previously treated urothelial cancer that worsened, despite platinum-based chemotherapy—nivolumab, avelumab, pembrolizumab, and durvalumab.<sup>50-53</sup> In a large clinical trial that led to the approval of pembrolizumab, patients who received the immunotherapy lived approximately 3 months longer than those who received chemotherapy. Meanwhile, the rate of serious treatment-related adverse effects was more than three times lower in the pembrolizumab group than in the chemotherapy group (15% v 49%).<sup>54</sup>

Recent clinical trials also point to the potential use of immunotherapy as an initial treatment for advanced bladder cancer. As a result of physical frailty and certain health conditions, up to two thirds of patients are not eligible for cisplatin-based chemotherapy,



**Table 2.** Notable Recent Advances With Immune Checkpoint Inhibitors

Cancer Type	Key Finding	First Author
Breast cancer	Addition of pembrolizumab to standard neoadjuvant therapy for high-risk, HER2-negative breast cancer increased rates of pathologic complete response, especially in women with triple-negative breast cancer—a 50% higher rate.	Nanda <sup>36</sup>
Head and neck cancer	Patients with recurrent or metastatic squamous cell head and neck cancer who received nivolumab lived a median of 2-3 months longer than did those who received standard therapy of investigator's choice.	Gillison <sup>37</sup>
Head and neck cancer	Compared with patients with recurrent or metastatic squamous cell head and neck cancer who received standard therapy of investigator's choice, those who received nivolumab had fewer symptoms and better quality of life for 15 weeks.	Harrington <sup>38</sup>
Kidney cancer	Response rate was higher in patients with advanced kidney cancer who received nivolumab as initial treatment than in those who received standard sunitinib (42% v 26%, respectively), and time until cancer worsening was longer (median, 11.6 months v 8.4 months, respectively).	Escudier <sup>39</sup>
Liver cancer	In an early clinical trial of patients with advanced liver cancer, response rate to nivolumab was 20%, and adverse effects were manageable.	El-Khoueiry <sup>40</sup>
Lung cancer	In a clinical trial of patients with advanced small-cell lung cancer, 1-year survival rate was 30% for those who received nivolumab and 42% for those who received nivolumab with ipilimumab.	Hellmann <sup>41</sup>
Lung cancer	Treatment with checkpoint inhibitor durvalumab after standard chemotherapy and radiation delayed worsening of stage III NSCLC by 11 months.	Antonia <sup>42</sup>
Skin cancer	Compared with patients with advanced melanoma who received adjuvant ipilimumab, those who received nivolumab had a higher rate of recurrence-free survival at 12 months (70% v 61%, respectively) and a lower rate of severe adverse effects (14% v 46%, respectively).	Weber <sup>43</sup>
Skin cancer	In patients with advanced melanoma, 3-year survival rate was higher with nivolumab and ipilimumab combined (55%) than with either nivolumab alone (52%) or ipilimumab alone (32%).	Wolchok <sup>44</sup>
Skin cancer	In a clinical trial of patients with advanced Merkel cell carcinoma, response rate to PD-L1 inhibitor avelumab was 32% during a median follow-up of 10 months.	Kaufman <sup>45</sup>
Skin cancer	An early clinical trial suggests that a new PD-1 inhibitor, REGN2810, may be effective against a common skin cancer, cutaneous squamous cell carcinoma. Response rate in patients with advanced disease was 52%.	Papadopoulos <sup>46</sup>
Stomach cancer	A large clinical trial shows that nivolumab is effective as a salvage therapy for people with advanced gastric or gastroesophageal junction cancer that worsens despite chemotherapy. At 12 months, 27% of patients were alive compared with 11% of those who received placebo.	Kang <sup>47</sup>
Stomach cancer	Pembrolizumab showed promising efficacy in a clinical trial of patients with previously treated, advanced stomach or gastroesophageal junction cancer. Response rate was 11%, and 12-month survival rate was 23%.	Fuchs <sup>48</sup>

Abbreviations: HER2, human epidermal growth factor receptor 2; NSCLC, non-small-cell lung cancer; PD-L1, programmed death-ligand 1.

which is the standard initial treatment of this disease. Alternative chemotherapies exist, but are less effective; therefore, many such patients receive only supportive care.

In 2017, the FDA granted accelerated approval to pembrolizumab for this indication.<sup>53</sup> The approval was based on a clinical trial of patients with locally advanced or metastatic urothelial cancer who were not eligible for cisplatin-containing

chemotherapy.<sup>55</sup> At a median follow-up of 8 months, treatment response rate was 28%, and responses lasted up to 18 months (median duration not reached). Pembrolizumab was well tolerated, with serious adverse effects occurring in 18% of those treated.

In another clinical trial, atezolizumab also was proven to be effective as an initial therapy for patients with advanced urothelial cancer who cannot receive cisplatin-containing chemotherapy.<sup>56</sup>

**Table 3.** Recent US Food and Drug Administration Approvals of Immunotherapies for Bladder Cancer

Drug Name (trade name)	Indication	Date Approved
Atezolizumab (Tecentriq; Genentech Oncology, South San Francisco, CA)	For treatment of patients with locally advanced or metastatic urothelial carcinoma who experience progression during or after platinum-containing chemotherapy or within 12 months of treatment with platinum-containing chemotherapy.	May 2016
Nivolumab (Opdivo; Bristol-Myers Squibb, Sunnyvale, CA)	For treatment of patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or who experience disease progression within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing chemotherapy.	February 2017
Avelumab (Bavencio; EMD Serono, Darmstadt, Germany)	For patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.	May 2017
Durvalumab (Imfinzi; AstraZeneca, London, United Kingdom)	For treatment of patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or who experience disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.	May 2017
Pembrolizumab (Keytruda; Merck & Co, Kenilworth, NJ)	For patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.	May 2017



At a median follow-up of 18 months, the treatment response rate was 23% and median survival was nearly 16 months. These advances have defined new standards of care for patients with advanced bladder cancer.

### A Policy Focus: Promoting Patient Participation in Clinical Trials

Clinical trials are critical for the advancement of new cancer treatments, but only a small percentage of patients (< 3%) in the United States participate in clinical trials.<sup>57</sup> In clinical trials, eligibility criteria define the trial population and protect the safety of trial participants, particularly those who may be more vulnerable to the adverse effects of treatment in a clinical trial; however, overly restrictive eligibility criteria can make trial findings more difficult to apply to the treatment of real-world patients with cancer.

ASCO, in collaboration with the nonprofit advocacy organization, Friends of Cancer Research, issued a joint research statement calling for the use of more inclusive eligibility criteria for cancer clinical trials. The statement, published in *Journal of Clinical Oncology*, provides recommendations to address eligibility criteria in five areas: minimum age requirements for trial enrollment, patients with HIV/AIDS, patients with brain metastases, patients experiencing organ dysfunction, and patients with prior and concurrent malignancies.

ASCO is working with the FDA and clinical trial sponsors to identify additional opportunities to safely expand eligibility criteria for oncology trials.

### New Approaches Help People With Brain Cancer Live Longer

*Two new regimens extend survival in patients with glioblastoma.* Grade IV glioma, or glioblastoma (GBM), is one of the most common and deadliest types of brain cancer in adults. With current therapies, fewer than one in 10 patients live 5 years after a diagnosis of GBM. There are now two new strategies that can possibly lengthen life for people with GBM. For more information about GBM and other brain tumors, visit [Cancer.Net](http://Cancer.Net).

The first involves a novel technology known as tumor-treating fields (TTFs). These are low-intensity electrical fields that are thought to slow cancer growth by blocking cell division. TTFs are delivered to the brain tumor through the skin from a device that patients wear on their head continuously at least 18 hours a day. Preliminary findings from a clinical trial of TTFs led to the FDA approval of the device in 2015 for use in combination with temozolomide chemotherapy, after surgery, chemotherapy, and radiation, for patients with newly diagnosed GBM.<sup>58</sup>

In 2017, researchers reported longer follow-up findings from the same clinical trial.<sup>59</sup> The risk of death was reduced by 37% for patients who used the device compared with those who received chemotherapy alone, with a median survival of 21 months with TTFs and chemotherapy, versus 16 months with chemotherapy

alone. The addition of TTFs also doubled the 5-year survival rate, from 5% to 13%.

The second advance is the discovery that adding temozolomide chemotherapy to short-course radiotherapy results in longer survival than radiotherapy alone in elderly patients with GBM.<sup>60</sup> The prognosis for elderly patients with GBM is poor and questions remain about the optimal treatment of older patients.

In the study, patients who received temozolomide with radiotherapy had a 33% lower risk of death and lived longer than those who received radiotherapy alone (median, 9.3 months *v* 7.6 months, respectively), whereas quality of life was similar between the two groups. Researchers also confirmed prior findings that suggested that a genomic biomarker, methylation of the O6-methylguanine–DNA methyltransferase (*MGMT*) gene, predicts better outcomes in patients with GBM. Among patients with methylated *MGMT*, median survival with radiotherapy plus temozolomide was 13.5 months compared with 7.7 months with radiotherapy alone.

*Adding chemotherapy to radiation slows glioma growth.* Grade III glioma, or anaplastic glioma, commonly occurs in young adults. This type of brain tumor can grow quickly and can recur as GBM despite treatment.

For patients with anaplastic glioma with a genomic abnormality known as 1p19q codeletion (loss of chromosome arms 1p and 19q) there is clear evidence that adding chemotherapy to radiation therapy improves survival; however, there are conflicting reports of the value of adjuvant (postsurgery) chemotherapy for anaplastic glioma without 1p19q codeletion. Preliminary findings from a large clinical trial have clarified the role of adjuvant temozolomide in this patient population.<sup>61</sup>

The 5-year survival rate was markedly longer when temozolomide was added to radiation therapy (56%) than when patients received radiation therapy alone (44%). Addition of temozolomide after radiation therapy delayed disease worsening by > 2 years (median, 43 months *v* 19 months, respectively). Temozolomide was well tolerated, with serious adverse effects occurring in only 12% of patients. These findings have established this regimen as a new standard of care for patients with anaplastic glioblastoma without 1p19q codeletion.

### New Targeted Therapy Regimens for Breast Cancer

*For BRCA-related breast cancer, olaparib is more effective than chemotherapy.* Findings from a large clinical trial of women with advanced, BRCA-related breast cancer point to a new type of treatment for the disease—poly (ADP-ribose) polymerase (PARP) inhibitors. Compared with standard chemotherapy, the PARP inhibitor olaparib lowered the risk of cancer worsening by 42% and extended the time until the cancer worsened by approximately 3 months.<sup>62</sup> Severe adverse effects were less common with olaparib, occurring in 37% of patients compared with 50% of those who were treated with chemotherapy. For more information about advanced breast cancer, visit [Cancer.Net](http://Cancer.Net).

Whereas several PARP inhibitors are already approved by the FDA for the treatment of ovarian cancer, this is the first study to demonstrate clinical benefit from this approach in patients with breast cancer. Several other large clinical trials of olaparib in breast cancer are underway ([ClinicalTrials.gov](http://ClinicalTrials.gov) identifiers: NCT02032823 and NCT03167619).



Up to 3% of all breast cancers occur in women who carry inherited changes in genes *BRCA1* and *BRCA2*. These changes undermine the ability of the cell to repair damaged DNA. Because of their underlying defect in DNA repair, cancer cells with *BRCA* mutations are particularly vulnerable to treatments that target PARP, another key component of the cell's DNA repair machinery.

*Dual targeted therapy lowers the risk of invasive breast cancer in some women.* A clinical trial of nearly 5,000 women with early, human epidermal growth factor receptor 2 (HER2)-positive breast cancer has suggested that adding a second HER2-targeted medicine, pertuzumab, to the standard regimen of the HER2-blocking therapy trastuzumab and chemotherapy may help some women.<sup>63</sup>

Recurrences were reduced by approximately one fifth in patients who received pertuzumab with trastuzumab after surgery compared with those who received trastuzumab and placebo. At 3 years, an estimated 94.1% of patients in the pertuzumab group were free of invasive breast cancer compared with 93.2% of patients in the placebo group. Addition of pertuzumab did not increase the rate of heart problems, which is the greatest concern with HER2-targeted therapy.

Treatment benefit was particularly evident in patients with breast cancer that had spread to lymph nodes—an estimated 92% were free of invasive cancer compared with 90.2% of those who received placebo at 3 years. In contrast, in patients with node-negative cancer, pertuzumab did not improve invasive disease-free survival.

These findings may set a new standard of care for some patients with node-positive, HER2-positive, hormone receptor-negative breast cancer who have a higher risk of developing invasive breast cancer. Meanwhile, researchers are trying to identify biomarkers that may help predict which groups of patients will benefit most from pertuzumab. The good news from this trial is that patients with HER2-positive breast cancer—the group of patients that used to have the worst prognosis—are doing so well on trastuzumab alone.

### **Research Supports Extended Hormone Therapy for Patients With Higher-Risk Breast Cancer**

To lower the chance of cancer recurrence, many women with early-stage breast cancer receive hormone therapy after surgery. Until recently, the recommended standard duration of such therapy had been 5 years, but new research findings suggest that extending hormone therapy may benefit some patients.

In 2016, a large clinical trial found that, in women with hormone receptor-positive, early breast cancer who received the aromatase inhibitor letrozole for 10 years, breast cancer recurrences or new cancers in the opposite breast were reduced by approximately one third compared with women who received 5 years of aromatase inhibitor therapy.<sup>64</sup> Later that year, an even larger trial reported a similar (29%) reduction in the risk of breast cancer recurrence or cancer in the opposite breast for women who received 5 additional years of letrozole after 5 years of aromatase inhibitor therapy (this study was funded, in part, by a grant from the NCI).<sup>65</sup> However, longer hormone therapy did not improve overall or disease-free survival—the primary end point of the

study—and was accompanied by a small increase in the risk of blood clots.

In late 2017, researchers reported on an improvement in disease-free survival for women who received extended aromatase inhibitor therapy after tamoxifen.<sup>66</sup> In that clinical trial, 5-year disease-free survival was 83% among women who received anastrozole for 6 years, and 79% among those who received it for 3 years; however, patients in the 6-year therapy group had more adverse effects, including joint and muscle pain.

Taken together, these findings support longer hormone therapy for women with early breast cancer who have a higher risk for recurrence on the basis of tumor features and patient-specific factors. Discussion of therapy duration should take into consideration the adverse effects the patient experienced during initial hormone therapy, as well as ongoing health conditions. If patients are carefully selected for extended hormone therapy, breast cancer mortality can be additionally reduced without overtreatment.

### **Bevacizumab May Help Some Women With Ovarian Cancer Live Longer**

Women with recurrent ovarian cancer have a short life expectancy and limited treatment options. In late 2016, the FDA approved a new regimen that improves their outlook—adding bevacizumab to standard platinum-based chemotherapy. This was the first approval of a new treatment of platinum-sensitive ovarian cancer in more than a decade. Bevacizumab had been previously approved for the treatment of women with platinum-resistant ovarian cancer. For more information about ovarian cancer, visit [Cancer.Net](http://Cancer.Net).

This new approval was based on a clinical trial in which women received standard chemotherapy alone or bevacizumab with standard paclitaxel plus carboplatin chemotherapy, followed by maintenance therapy with bevacizumab (this study was funded, in part, by a grant from the NCI).<sup>67</sup> Addition of bevacizumab significantly extended median time until cancer worsening to 13.8 months compared with 10.4 months with chemotherapy alone. Overall survival was also longer with bevacizumab than with chemotherapy alone (median, 42 months *v* 37 months), but this difference was not statistically significant; however, the rate of severe adverse effects was higher in the bevacizumab group (96%) than in the standard therapy group (86%), with high blood pressure and fatigue being the most common adverse effects with bevacizumab.

### **New Maintenance Therapies Keep Recurrent Ovarian Cancer From Worsening**

Maintenance therapy for ovarian cancer is critical because of the high rate of recurrence, despite initial response to standard platinum-based chemotherapy. In 2017, the FDA approved a new maintenance treatment, the PARP inhibitor olaparib, for women with recurrent ovarian cancer who responded to platinum-based chemotherapy.<sup>68</sup> Approval was based on a clinical trial in which olaparib was demonstrated to markedly slow cancer growth.<sup>69</sup> Median time until cancer worsening was 19.1 months with olaparib versus 5.1 months with placebo. The most common severe adverse effects of olaparib were anemia and fatigue.



Meanwhile, in a clinical trial of maintenance therapy with the PARP inhibitor rucaparib, the growth of platinum-sensitive, recurrent ovarian cancer was also slowed.<sup>70</sup> Overall, rucaparib delayed cancer worsening by approximately 5 months longer than placebo (10.8 months *v* 5.4 months, respectively). Benefit was greatest among women with *BRCA* mutations (median time until cancer worsening was 16.6 months with rucaparib *v* 5.4 months with placebo), as well as women with tumors that harbored defects in DNA repair machinery (median time until cancer worsening was 13.6 months with rucaparib *v* 5.4 months with placebo). The most common severe adverse effects of rucaparib were anemia and liver enzyme abnormalities. These findings have been submitted to the FDA for the approval of rucaparib in this setting.

### A Policy Focus: Learning More About Older Adults With Cancer

More than 60% of cancer diagnoses in the United States occur in people age  $\geq 65$  years—a population that will grow rapidly over the coming years. Whereas 70% of cancer deaths occur in older adults, and older adults make up the majority of survivors of cancer, the evidence base for treating this population is sparse. Older adults are under-represented in clinical trials, and trials designed specifically for older adults are rare.

ASCO and the FDA held a workshop in November 2017 to discuss ASCO's recommendations to improve the evidence base for treating older adults. ASCO is continuing to urge federal agencies and the cancer research community to increase the enrollment of older adults in clinical trials and use other strategies to collect evidence on this population of patients.

### Precision Medicine Helps People With Melanoma Live Longer

Whereas early-stage melanoma is curable with surgery, patients with stage III melanoma face a much higher chance of recurrence after surgery, and many ultimately die of metastatic disease. New findings suggest that a precision medicine approach that combines two targeted medicines can improve outcomes for a subset of patients.

The study was conducted in patients with tumors that harbored *BRAF* gene mutations, which occur in approximately 40% of all melanomas. *BRAF* mutations turn on a molecular pathway known as mitogen-activated protein kinase. Prior research has demonstrated that blocking this pathway with two medicines in combination—dabrafenib and trametinib—helps patients with metastatic, *BRAF*-mutated melanoma live longer (the FDA approved this regimen in 2014).

In 2017, researchers reported that the combination of dabrafenib and trametinib can also help patients with stage III melanoma by lowering the risk for recurrence after surgery.<sup>71</sup> Estimated 3-year relapse-free survival rates were 58% with targeted therapy and 39% with placebo. Overall survival rates were 86% with targeted therapy versus 77% with placebo.

Combined targeted treatment was associated with a considerable rate of serious adverse effects (36%), including potentially fatal pneumonia. Overall, 26% of patients had to stop treatment earlier than the planned 12-month duration as a result of adverse effects. Currently, there is insufficient evidence to inform the most beneficial duration of adjuvant therapy for stage III melanoma. For more information about melanoma, visit [Cancer.Net](http://Cancer.Net).

### New Treatment Paradigms Help Men With Prostate Cancer Live Longer

*Adding hormone therapy to radiation boosts the long-term survival rate.* More than 30% of men who receive surgery for localized prostate cancer experience a recurrence of cancer. Patients who experience a local recurrence after surgery receive radiation therapy, but despite the therapy, the cancer eventually worsens in up to 50% of men. For more information about prostate cancer, visit [Cancer.Net](http://Cancer.Net).

A recent large clinical trial found that adding androgen-deprivation therapy to radiation therapy helps men, who experience a local recurrence after surgery, live longer (this study was funded, in part, by a grant from the NCI).<sup>72</sup> The study enrolled men with prostate-specific antigen levels between 0.2 ng/mL and 4 ng/mL at least 8 weeks after surgery. Men were randomly assigned to receive androgen-deprivation therapy bicalutamide during and 24 months after radiation therapy or radiation therapy and placebo. Survival rate at 12 years was 76% in the bicalutamide group versus 71% in the placebo group. More men in the placebo group developed metastatic prostate cancer (23% *v* 14%, respectively) and more died of the disease (13% *v* 6%, respectively). Late effects of radiotherapy were similar between groups, but gynecomastia (swelling of breast tissue) was much more common with bicalutamide, occurring in 70% of men compared with 11% of those who received placebo.

Whereas other clinical trials are investigating the use of newer hormonal therapies with radiation therapy after prostate cancer surgery ([ClinicalTrials.gov](http://ClinicalTrials.gov) identifiers: NCT00541047 and NCT00423475), these findings provide strong evidence to support the combination of androgen-deprivation therapy with radiation therapy for men who experience a local recurrence after surgery.

*A new standard of care for advanced prostate cancer.* Two large studies presented in 2017 demonstrated that adding abiraterone to standard androgen-deprivation therapy helps men with metastatic prostate cancer live longer. Whereas androgen-deprivation therapy slows prostate cancer growth by preventing the testicles from making testosterone, certain other organs in the body continue making small amounts of testosterone and other androgens. Abiraterone stops the production of both testosterone and other androgens throughout the body by blocking an enzyme that converts other hormones to androgens.

In the first study, patients with high-risk metastatic prostate cancer were randomly assigned to receive androgen-deprivation therapy with either abiraterone or placebo.<sup>73</sup> At a median follow-up of 30 months, men who received abiraterone had a 38% lower risk of death than did those who received placebo. Abiraterone also more than doubled the median time until cancer worsening from 15 months to 33 months.



The second study, which included men with high-risk, locally advanced or metastatic prostate cancer, found that patients who received abiraterone with standard androgen-deprivation therapy had a 37% lower risk of death than those who received androgen-deprivation therapy alone.<sup>74</sup> The 3-year survival rate was 76% with standard therapy alone and 83% with standard therapy plus abiraterone.

Taken together, these findings define a new standard of care for men with metastatic prostate cancer.

### **Research Informs Decision Making for Early Prostate Cancer Treatment**

Men with early (localized) prostate cancer can choose one of three standard treatments, which include surgery, radiation therapy, or active surveillance. A recent clinical trial found no significant differences in 10-year survival with any approach, although active surveillance was associated with a higher risk of cancer worsening and metastasis.<sup>75</sup>

A subsequent analysis of patient-reported outcome data from the same clinical trial showed that adverse effects differed among the three approaches.<sup>76</sup> Surgery had a greater negative impact on sexual function and urinary continence than either radiation therapy or active surveillance. In the active surveillance group, sexual and urinary function declined gradually. Bowel function problems were worse in the radiotherapy group than in the other two groups at 6 months, but subsequently recovered somewhat. There were no significant differences among the treatment groups in anxiety, depression, or general health-related or cancer-related quality of life.

Another clinical trial that compared surgery with active surveillance found that men who received surgery had more sexual dysfunction and urinary incontinence through 10 years than did those who received active surveillance (this study was funded, in part, by grants from the US Department of Veterans Affairs, the Agency for Healthcare Quality and Research, and the NCI).<sup>77</sup> Limitations in activities of daily living through 2 years were also greater in the surgery group.

In addition, two large, population-based studies that observed men with localized prostate cancer for 3 years also found that patterns of adverse effects differed depending on the type of treatment men received.<sup>78,79</sup>

Taken together, these findings from clinical trial participants as well as real-world patients will help clinicians better counsel patients about the risks and benefits of various treatments for localized prostate cancer.

### **Less Is More: Preserving Quality of Life With Less Treatment**

*Shorter chemotherapy for colon cancer is safe and lowers the chance of nerve damage.* For patients with stage III colon cancer, administering chemotherapy after surgery (adjuvant chemotherapy) lowers the chance that the cancer will come back. The standard 6-month course of adjuvant oxaliplatin-based chemotherapy can cause peripheral neuropathy. Symptoms of this condition, which include pain, tingling, numbness, and muscle weakness, sometimes persist indefinitely. Longer chemotherapy also typically means more diarrhea and fatigue, more doctor

appointments, blood draws, and time away from work and social gatherings.

Six clinical trials with 12,800 patients in North America, Europe, and Japan explored whether adjuvant chemotherapy regimens that consisted of either FOLFOX (infusional fluorouracil, leucovorin, and oxaliplatin) or CAPOX (capecitabine and oxaliplatin) could be shortened to 3 months without compromising survival. In 2017, researchers reported on the analysis of pooled data from the trials (this study was funded, in part, by a grant from the NCI).<sup>80</sup>

The chance of being free from colon cancer at 3 years was only slightly lower with 3 months of chemotherapy than with 6 months (74.6% v 75.5%, respectively). For patients with a lower risk of cancer recurrence (T1 to T3 N1 colon cancer), the chance of being cancer free at 3 years was nearly identical between the two groups—83.1% in those who received a 3-month course and 83.3% in patients who received a 6-month course.

The rate of clinically meaningful nerve damage differed depending on the type of chemotherapy regimen received, but was consistently lower for people who received 3 months versus 6 months of chemotherapy (15% v 45% with FOLFOX and 17% v 48% with CAPOX, respectively).

These findings, relevant to approximately 400,000 patients with stage III colon cancer worldwide, should inform conversations between oncologists and their patients. For patients with lower-risk stage III colon cancer, the shorter 3-month course will likely become the new standard of care. For patients with higher-risk cancer, decisions on shorter-duration therapy will have to be carefully weighed against the risks of recurrence, patient ability to tolerate chemotherapy, and patient preferences. For more information about colon cancer, visit [Cancer.Net](#).

*Less extensive surgery for melanoma spares patients complications.* Many patients with intermediate-thickness melanomas (1.2 mm to 3.5 mm) routinely receive sentinel lymph node biopsy, a procedure that removes the first lymph node to which cancer cells are likely to spread. The lymph node is then checked for cancer. If cancer cells are found in this sentinel node, the patient is more likely to experience a recurrence of melanoma after surgery.

To lower the chances of recurrence in patients with cancer in sentinel nodes, removal of the remaining lymph nodes near the tumor is usually recommended; however, this more extensive surgery increases the risk for complications, particularly long-term swelling of an arm or leg from the build-up of lymph fluid in tissues, known as lymphedema. Experts have therefore questioned the value of this surgical procedure in patients with positive sentinel lymph nodes.

A large clinical trial reported in 2017 suggests that the removal of additional lymph nodes may not be necessary (this study was funded, in part, by a grant from the NCI).<sup>81</sup> At 3 years, the rate of melanoma-specific survival (the percentage of people who had not died of melanoma) was the same (86%) whether patients received additional surgery to remove lymph nodes or were only observed.

Patients who received additional surgery had a lower risk of regional recurrence, but also had more health complications. The rate of lymphedema was four times higher in the surgery group than in the observation group (24% v 6%, respectively). Given that lymph node surgery does not improve survival, it



may be possible to avoid this treatment in many patients and spare them an additional surgery with its associated complications.

### A Policy Focus: Streamlining Adverse Events Reporting for Cancer Clinical Trials

Regulations require research sponsors to report certain serious adverse events experienced by patients in a clinical trial to the FDA via an expedited process. The current challenge with reporting is the high volume of uninformative reports, which hinders patient safety, imposes a substantial toll on the FDA, research site time, and resources. In March 2017, ASCO held a workshop on streamlining adverse events reporting. Attended by stakeholders from across the cancer research community, including researchers, industry representatives, patient advocates, and officials from the FDA and the NCI, the workshop discussed ways to decrease over-reporting as well as best practices for adverse events reporting for both sponsors and research sites. Recommendations developed through this effort were published in late 2017 in *Journal of Clinical Oncology*.

*Fewer women having additional breast surgery after lumpectomy.* Performing a second surgery after initial lumpectomy for early breast cancer was previously common. Second surgery was often recommended as a result of positive or close margins, which means that some cancer cells were found along the edge of the cancer tissue removed by lumpectomy; however, there has been controversy over what constitutes a negative margin.

In 2014, the Society of Surgical Oncology and the American Society of Radiation Oncology published an evidence-based consensus statement, endorsed by ASCO, that recommended that if there are no cancer cells adjacent to any inked edge/surface of the surgical specimen, the margins should be considered negative and a second surgery is not required.<sup>82</sup>

A recent large, population-based study assessed the effect of this recommendation on the rates of breast cancer surgery (this study was funded, in part, by a grant from the NCI).<sup>83</sup> From 2013 to 2015, the rate of initial lumpectomy remained stable at 67%, but the rate of second breast surgery declined by 16%, and fewer women underwent a subsequent mastectomy. This study demonstrates the important role of clinical practice guidelines in reducing overtreatment.

*Delaying rectal cancer surgery lowers the risk of complication.* Radiation therapy before surgery lowers the risk of local recurrence in patients with rectal cancer. In the past, it was considered important to perform surgery soon after the completion of radiation therapy, but a new study in Sweden found that delaying surgery by a few weeks is safe and results in fewer complications.<sup>84</sup>

There was no difference in local recurrence between patients who received the standard short-course radiation therapy with

surgery within 1 week and those who received surgery 4 weeks to 8 weeks after either short-course radiation or long-course radiation therapy. Patients who received short-course radiation therapy with delayed surgery had a nearly 40% lower risk of complications after surgery than those who received standard short-course radiation without a delay in surgery.

Although common in Europe, short-course radiation therapy before surgery is not used in the United States, where the standard approach is chemotherapy and radiation. An ongoing clinical trial is exploring whether radiation therapy can be eliminated from the treatment of high-risk, locally advanced rectal cancer ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01515787) identifier: NCT01515787).

*Lowering radiation therapy dose for throat cancer reduces long-term complications.* HPV-associated oropharyngeal cancer responds well to treatment, but the standard radiation therapy administered with chemotherapy can lead to debilitating long-term complications. As patients with HPV-associated oropharyngeal cancer tend to be younger, they may carry the burden of these complications for decades.

Two separate clinical trials found that lowering the standard radiation dose by 15% to 20% in patients with a favorable prognosis (ie, a complete clinical response is achieved with initial chemotherapy) does not compromise survival. In the first study, the 2-year survival rate was 94% for patients who were treated with 54 Gy and 96% for those who received  $\leq 54$  Gy, and adverse effects were milder with the lower dose (this study was supported, in part, by grants from the NCI and the US Department of Health and Human Services).<sup>85</sup> At 12 months, markedly fewer patients in the lower-dose group had difficulty swallowing solids (40% v 89%, respectively) or impaired nutrition (10% v 44%, respectively) compared with patients who received higher doses of treatment. In the second study, where patients with a more favorable prognosis received a dose of 54 Gy and others received 60 Gy, cancer had not worsened for 92% of patients overall at 2 years.<sup>86</sup>

If confirmed in a larger clinical trial, these findings will lead to a change in the standard of care for patients with lower-risk, HPV-related oropharyngeal cancer (eg, those with a minimal smoking history and small tumor size). For more information about oropharyngeal cancer, visit [Cancer.Net](http://Cancer.Net).

### Recent ASCO Clinical Practice Guidelines

Clinical practice guidelines help to distill knowledge about a particular clinical issue and provide recommendations to help clinicians deliver the best treatment and care to every patient. ASCO develops its clinical practice guidelines through a rigorous, systematic review of relevant medical literature and clinical interpretation from a multidisciplinary panel of experts and patient representatives. In 2017, ASCO issued more than 14 clinical practice guidelines, guideline updates, and provisional clinical opinions (Table 4). To view ASCO guidance by clinical area, visit <https://www.asco.org/practice-guidelines/quality-guidelines/guidelines>.



**Table 4.** ASCO Clinical Practice Guidelines, Updates, Endorsements, and Provisional Clinical Opinions from January to October 2017

Publication Date	Guideline
Guideline	
January 17	Management of Small Renal Masses: American Society of Clinical Oncology Clinical Practice Guideline Summary
January 30	Screening to Prevent Invasive Cervical Cancer: ASCO Resource-Stratified Clinical Practice Guideline
February 6	Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology
March 6	Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline
March 17	Primary Prevention of Cervical Cancer: American Society of Clinical Oncology Resource-Stratified Guideline
August 10	Treatment of Nonmetastatic Muscle-Invasive Bladder Cancer: American Urological Association/American Society of Clinical Oncology/American Society for Radiation Oncology/Society of Urologic Oncology Clinical Practice Guideline
September 11	Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline
Guideline Update	
March 27	Brachytherapy for Patients With Prostate Cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update
April 11	Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update
April 24	Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stages I to IIIA Resectable Non–Small-Cell Lung Cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline Update
July 10	Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update
July 31	Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update
August 14	Systemic Therapy for Stage IV Non–Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update
Guideline Endorsement	
February 27	Head and Neck Cancer Survivorship Care Guideline: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Cancer Society Guideline
Provisional Clinical Opinion	
April 25	Second-Line Hormonal Therapy for Men With Chemotherapy-Naïve, Castration-Resistant Prostate Cancer: American Society of Clinical Oncology Provisional Clinical Opinion

For additional advances in cancer treatment, please see Appendix [Table A1](#) (online only).

## ADVANCES IN PATIENT CARE

### **Communication and Coping Tools Improve End-of-Life Planning**

Having accurate information about prognosis is crucial for patients with late-stage cancer. Having conversations about the end of life helps patients set appropriate goals and potentially avoid intensive medical treatments and hospital death.

However, many patients are misinformed about or misunderstand their prognosis, and others have difficulty coping with the realization that their illness is terminal. Recent research has focused on interventions and tools that may help overcome this gap in patient-doctor communication.

In one study, a communication coaching intervention helped patients with late-stage cancer actively seek information and express preferences about their care (this study was funded, in part, by a grant from the NCI).<sup>87</sup> Oncologists in the intervention group received brief, individualized, skill-based communication training that focused on being receptive to patient questions and concerns. Patients received individualized communication coaching that incorporated a list of questions related to cancer care and end-of-life issues. Oncologists and patients in the control group did not receive any communication training or prompting.

During a subsequent office visit, nearly three times as many patients in the intervention group than in the control group (17% *v* 6%, respectively) asked about prognosis, and more than twice as many (70% *v* 33%, respectively) brought up topics that were

covered by the communication coaching, such as cancer treatment, current cancer state, and preferences about care at the end of life. Whereas validation of these results in other settings is necessary, they underscore the value of combined patient–doctor interventions to enhance communication.

New online tools are another way of helping patients plan for the end of life. In a recent study of elderly patients with chronic and/or serious conditions, 35% of those who used the interactive, patient-centered advance care planning Web site, PREPARE, along with an easy-to-read advance directive, succeeded in assembling advance planning documentation compared with 25% of those who used the advance directive alone (this study was funded by a grant from the US Department of Veterans Affairs Office of Research and Development).<sup>88</sup> Given that the Web site used in this study is free to the public and requires no physician involvement, it represents a method of improving end-of-life care with minimal health care system resource expenditure.

Research shows that certain coping strategies can help patients with incurable cancer who accurately understand their diagnosis to be terminal (this study was funded, in part, by grants from the NIH, NCI, and the National Institute of Nursing Research).<sup>89</sup> For example, patients who used positive reframing (ie, looking for something good in their situation) and active coping (ie, taking action to try to make their situation better) had improved quality of life and less depression.

It is important that doctors communicate the availability of these tools and help patients both understand and cope with advanced cancer and a terminal prognoses. A new ASCO guideline provides oncologists with recommendations regarding core communication skills that apply across the continuum of cancer care, including discussion of goals of care and prognosis, treatment



selection, and end-of-life care.<sup>90</sup> For more information on coping with cancer, visit [Cancer.Net](http://Cancer.Net).

### CancerLinQ Partners With Federal Agencies and Medical Specialty Societies

In 2017, one of the main focus areas for CancerLinQ was partnering with federal agencies, professional societies, and life sciences companies. The goal of these collaborations was to convene the cancer community around solutions for improving the quality of care for patients with cancer. By leveraging the expertise of the many stakeholders that span the care continuum, all of whom affect key decision points in a patient's care, we can help make CancerLinQ a system that encompasses all of cancer care. The effort was successful, with 10 collaborations formally signed and announced between June 2016 and June 2017 with the following organizations:

- American Academy of Physician Assistants
- American Society of Radiation Oncology
- Cancer Informatics for Cancer Centers
- College of American Pathologists
- US Food and Drug Administration
- Hematology/Oncology Pharmacy Association
- National Comprehensive Cancer Network
- National Cancer Institute
- Oncology Nursing Society
- Society of Gynecologic Oncology

The organizations with which CancerLinQ has partnered are invited to participate in the CancerLinQ Oncology Leadership Council, the official body of strategic advisors that comprise member representatives from CancerLinQ's official partner organizations and advisory groups. This is the first time that a coalition of this nature has been created and convened. As CancerLinQ creates this community of learning in cancer, these foundational partners offer incredible thought leadership and represent the importance of a team-based approach to delivering high-quality care.

### Managing Common Adverse Effects and Complications

*Radiation therapy for lung cancer increases the risk for heart problems.* Radiation has been the backbone of treatment of stage III NSCLC for three decades. Despite the known harmful effects that chest radiation can have on the heart, patients with stage III NSCLC still receive high doses of radiation because it is believed that few live long enough to experience heart complications (life

expectancy is < 2 years). A pair of studies published in 2017 challenge this notion by showing that heart problems are relatively common in this patient population and occur earlier than historically understood.

In an analysis of patients who were treated in six clinical trials from 1996 to 2009, 21% of those who received a high dose of radiation ( $\geq 20$  Gy) developed symptomatic heart problems within 2 years (this study was funded by a grant from the NIH).<sup>91</sup> Heart problems were independently linked to high doses of radiation and underlying risk (eg, smoking and cardiovascular disease).

A second analysis of patients who were treated in four clinical trials from 2004 to 2013 demonstrated similar results; 11% developed severe heart problems within 2 years (this study was funded by a grant from the NIH).<sup>92</sup> As in the other study, patients who received a higher radiation dose and/or had pre-existing heart disease were more likely to develop heart problems. Furthermore, both cancer worsening and heart problems were linked to shorter survival.

These findings will inform treatment and survivorship discussions between physicians and patients with stage III NSCLC. When selecting radiation dose, controlling tumor growth should be balanced with minimizing the risk for heart problems, particularly in patients with an underlying risk of heart disease.

A recent guideline from ASCO recommends that, before the start of therapy, doctors should discuss the potential for heart problems with patients who are at increased risk for such complications and establish a tailored and detailed plan to monitor them during and after cancer treatment.<sup>93</sup>

*Single radiation treatment relieves symptoms of spinal cord compression.* As many as one in 10 people with advanced cancer develops spinal cord compression. This condition is a major detriment to quality of life, causing back pain, numbness, tingling, difficulty or inability to walk, and sometimes bowel or bladder incontinence. Radiation therapy can prevent or relieve these symptoms, but it typically requires multiple trips to the clinic for treatment.

Research presented in 2017 demonstrated that a single radiation treatment may be sufficient for patients with a short life expectancy.<sup>94</sup> In a large clinical trial, one-time radiation treatment was as effective as 5 days of treatment in terms of helping patients stay mobile, and median survival was not different between the two groups (approximately 3 months). Shortening radiation therapy allows patients with cancer-related spinal cord compression to spend less time in the hospital and more time doing things they enjoy.

*For cancer-related fatigue, exercise and psychological support work best.* Cancer-related fatigue is different from feeling tired after staying up too late. It is a persistent feeling of physical, emotional, or mental exhaustion that interferes with one's daily activities and does not improve with rest. Most people who receive cancer treatment experience fatigue, and approximately one third of survivors of cancer experience fatigue that lasts for years after finishing treatment.

Numerous approaches for treating cancer-related fatigue have been tested, with variable outcomes; therefore, it has not been clear which treatments work best. An analysis of 113 randomized clinical trials compared the four most commonly recommended



treatments, which are exercise, psychological intervention, combined exercise and psychological intervention, and medication (this study was funded in part by grants from the NIH).<sup>95</sup>

Exercise, psychological support, and the combination of the two approaches improved cancer-related fatigue during and after cancer treatment. Benefits of these treatments were greater for patients with nonmetastatic disease and varied by intervention mode and timing; however, medications were much less effective than behavioral interventions.

These findings confirm a large body of literature in the field and suggest that exercise and psychological interventions should be used before pharmaceutical interventions, which provide minimal benefit. These recommendations are relevant to many patients with cancer.

ASCO recommends that health care providers assess the patient's level of fatigue at diagnosis and repeat this assessment yearly and at any time there are symptoms of fatigue throughout treatment and into recovery.<sup>96</sup> For more information about cancer-related fatigue, visit [Cancer.Net](http://Cancer.Net).

### ASCO Launches Center for Research and Analytics

In June 2017, ASCO announced the launch of its new Center for Research and Analytics (CENTRA) to make an array of cancer data available to the oncology community and provide consultation and support for research and analysis. The CENTRA team will help analyze and build an evidence base that can help to support cancer policy development, advance the practice of oncology, and improve cancer care for patients. This supports ASCO's continuing commitment to helping to advance the field of oncology and improve cancer care through the generation and application of high-quality evidence.

Requests can be made through CENTRA for data from ASCO sources, such as our quality programs, annual census of oncology practices, and scientific meeting abstracts and presentations. All research requests will be evaluated before being fulfilled.

For more information or to submit requests, please contact [CENTRA@asco.org](mailto:CENTRA@asco.org).

### Patient Engagement Leads to Improved Care

*Web-based symptom reporting extends survival.* The value of patients reporting their own outcomes is increasingly recognized in oncology, and there is interest in integrating patient-reported outcomes into routine practice. A recent study demonstrated that a Web-based, patient-reported outcomes tool can help patients with advanced cancer live longer.<sup>97</sup>

With the standard approach of assessing symptoms only during office visits, the health care team can be unaware of patients' symptoms up to half of the time. In a clinical trial, the Web-based tool enabled patients to report common symptoms in real time and triggered alerts to clinicians if symptoms worsened (this study was

supported by ASCO's Conquer Cancer Foundation). When appropriate, clinicians took action to relieve symptoms, such as lowering the chemotherapy dose or providing supportive care.

Patients with metastatic cancer who used the tool while receiving chemotherapy lived a median of 5 months longer than those who did not use the tool (31 months v 26 months, respectively). This improvement in survival was greater than that associated with nearly all cancer drugs that received FDA approval in 2016.

Researchers previously reported that the use of the same tool was associated with better quality of life and fewer visits to the emergency room and hospitalizations. The findings confirm that patient-reported outcomes should be the standard of care for patients with late-stage cancer. A nationwide clinical trial that uses an updated tool that works on both personal computers and mobile devices is under way in community practices across the United States.

*After cancer diagnosis, an online support program lowers distress.* Patients experience major distress when they first learn of their cancer diagnosis. Yet amid all the tests, treatment appointments, and family or work decisions, little attention is paid to one's psychological and emotional well-being. In fact, as a result of patients' time constraints and the lack of availability and resources for psychological support, few patients who are newly diagnosed with cancer receive any psychological support.

To address this need, researchers are looking into leveraging Internet-based technologies to provide support to more patients and improve their quality of life. In a recent study, an 8-week Web-based stress management program that was designed by psychologists and oncologists improved quality of life and lowered distress for patients who were newly diagnosed with cancer.<sup>98</sup>

The program covered different topics, such as bodily reaction to stress, cognitive stress reduction, feelings, and social interactions. For each weekly topic, participants received written and audio information, then completed exercises and questionnaires.

The study demonstrated that delivering psychological support via an Internet-based program is feasible, but more research is needed to refine and scale up such an approach for broad use. Researchers already have plans to translate the program into other languages (it is currently available only in German).

*Crowdsourcing advances cancer research.* Progress against rare cancers is often slow because of a combination of scarce funding and a limited availability of patients and tumor samples for research. An attractive solution to this problem is crowdsourcing. More and more people with rare and common cancers today have the opportunity to rapidly and directly affect research by sharing their tumor tissue samples and medical and/or genetic information to help others with the same or similar diseases. In return, researchers share what they learn with participants.

The Metastatic Breast Cancer Project collects health records and tumor and saliva samples to learn why some patients respond differently to cancer treatments than others. The project engages patients to participate via social media, newsletters, blogs, and advocacy organizations.

Two other such projects focused on sarcoma are run by researchers with the support of patient advocacy organizations, the Angiosarcoma Project and the Leiomyosarcoma Direct Research.

Another emerging type of crowdsourced research engages members of the general public, so-called citizen scientists, to gather ideas, design studies, and perform research-related tasks, such as



analysis of scientific images or quantitative data. This approach is particularly helpful in pathology research studies that require manual review of a large quantity of images. The Cell Slider project recruited approximately 100,000 people to classify images of breast tumor tissue according to estrogen receptor status. To assess the volunteers' performance, researchers compared their classification with that of trained pathologists and found that citizen scientists were able to classify tumors with high accuracy.<sup>99</sup> For additional notable advances in patient care, please see Appendix Table A1.

## LOOKING TO THE FUTURE

### ***New Type of Medicine Tackles Undruggable Molecular Targets***

Although targeted therapies have had a profound effect on cancer medicine, only approximately 20% of proteins in cancer cells can be targeted by currently available medicines. Many of the undruggable targets include important molecules in pathways that suppress (eg, TP53 and APC) or promote (eg, RAS and MYC) tumor growth. One of the reasons these targets are undruggable is that, historically, it has been difficult to block these pathways with small molecules, and protein drugs do not easily penetrate the cell.

A new class of drugs, known as stapled peptides, has emerged as a promising way to target protein-protein interactions. These small proteins have an artificial chemical bridge, or staple, that holds them in a specific shape that allows them to penetrate the cell.

In an early clinical trial, researchers demonstrated for the first time that a stapled peptide is effective in patients.<sup>100</sup> The peptide targeted the interaction between MDM2 and MDMX-TP53 in patients with solid tumors and lymphoma without p53 mutations. The treatment, ALRN-6924, stalled cancer growth in 45% of 55 patients. A larger clinical trial is under way ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02264613) identifier: NCT02264613).

### ***Emerging Role for Precision Medicine in Cancer Prevention***

The concept of precision medicine as applied to cancer prevention is in its nascent stages. In this first phase, scientists are focusing on inherited cancer syndromes, such as *BRCA*-related breast and ovarian cancers and Lynch syndrome.

For patients with inherited genetic susceptibility to cancer, the hope is to one day replace crude, one-size-fits all cancer risk reduction approaches, such as preventive surgery, with personalized approaches that take into account not only a person's genetic makeup and family history, but also the composition of microbes in their body, their diet, lifestyle, and environmental factors.<sup>101</sup>

Scientists are only beginning to understand how the complex interplay of all these factors raises or lowers the chance of developing cancer in an individual with an inherited cancer gene mutation. It is also not clear why changes in genes with broad functions, such as the DNA repair and MMR genes, predispose people for certain, but not all cancers.

Large-scale genomics studies are providing insights by which to fine-tune cancer risk assessment for each person. For example, it seems that certain changes in mitochondrial DNA lower the risk of breast cancer in patients with *BRCA* mutations. Genomic information, along with reproductive and family history, lifestyle,

and other factors, may help patients decide whether and when to have preventive surgery.

Scientists are also exploring the possibility of using immune-based approaches, such as vaccines for cancer prevention in healthy people with cancer predisposition syndromes.<sup>102</sup> The idea is to harness the immune system to recognize and eliminate pre-malignant cells on the basis of their molecular characteristics. With the new national investment in cancer prevention through the Cancer Moonshot initiative and cutting-edge technologies, such as sequencing the genomes of individual cells, the opportunity to advance this field is closer than ever.

### ***Understanding Health Disparities: Path to Better Care For All***

Cancer is becoming one of the most pressing health care challenges worldwide. Between 2005 and 2015, the number of patients with cancer increased worldwide by 33%.<sup>103</sup> According to the Global Burden of Disease study, issued in late 2017, cancer is the second leading cause of death from noncommunicable diseases, which cause 72% of deaths worldwide.<sup>25</sup>

Whereas many countries have experienced decreases in cancer mortality over the last decade, cancer deaths increased in Sub-Saharan Africa and certain other regions lacking in health care infrastructure (this study was funded in part by a grant from the NIH).<sup>103</sup> Seven of 10 cancer deaths occur in regions of Africa, Asia, and Central and South America, where access to cancer screening and treatment is limited.<sup>104</sup>

Even within high-resource countries, such as the United States, certain communities experience greater cancer incidence, shorter survival, and more deaths from cancer. During the last 60 years, socioeconomic, education, and racial/ethnic inequities in cancer mortality have persisted and even widened in some cases.<sup>105</sup>

#### **Impact of Cancer Care Cost**

Among Americans who have never had cancer, 35% are not confident they would receive timely, best-in-class care if diagnosed with cancer in the future. Of serious concern, 27% of Americans who either had cancer themselves or have/had a family member with cancer have taken specific actions to lower treatment costs:

- 9% have skipped doctor appointments;
- 8% have refused treatment;
- 8% have postponed filling or not filled prescriptions;
- 8% have skipped doses of prescribed medications; and
- 7% have cut pills in half.

(ASCO's National Cancer Opinion Survey, 2017).

Recently published studies reveal that the root causes of cancer disparities in the United States are complex. Researchers found that black patients across all socioeconomic groups have higher cancer mortality than white patients. Another study found that people from the poorest communities were more likely to be diagnosed with advanced cancer, regardless of whether they had health insurance.



### ASCO Issues Recommendations for Reducing Cancer Disparities Among Sexual and Gender Minority Populations

Sexual and gender minority (SGM) populations, including individuals who are lesbian, gay, bisexual, transgender, and intersex, bear a disproportionate cancer burden that stems from several factors, such as lower rates of cancer screening and a hesitancy on the part of SGM patients to disclose their sexual orientation to providers because of a fear of stigmatization. On April 3, 2017, ASCO issued recommendations to address the needs of SGM populations as they relate to cancer. The recommendations, published in a policy statement in *Journal of Clinical Oncology*, are designed to focus attention on the challenges that face the SGM community, including discrimination and greater risk of anxiety and depression, resulting in disparate care. The statement also provides concrete steps that can help minimize health disparities among SGM individuals.

### A Policy Focus: Giving Medicaid Patients Equal Access to Clinical Trials

Most private insurance plans and Medicare are required to cover the routine costs of care for patients who participate in clinical trials. Routine care includes items and services that a payer would cover for a patient who is not enrolled in a clinical trial, such as office visits, radiology exams, and laboratory tests; however, Medicaid is not required to cover these routine costs for patients.

For researchers to understand how different populations respond to cancer treatment and address disparities in cancer outcomes, all types of patients should have the opportunity to participate in cancer trials. Unfortunately, patients from racial and ethnic minority groups that are over-represented in the Medicaid program make up just a small subset of clinical trial participants.

ASCO strongly encourages policymakers to guarantee that Medicaid covers routine care costs for patients in clinical trials so that more patients with Medicaid can participate in cancer research.

In addition, patterns of disparity have been changing. For example, during the 1950s, black people had lower all-cancer mortality than did white people, but since the 1960s, all-cancer mortality rates have been significantly higher for black people than for white people across all socioeconomic groups. Differences are particularly pronounced for some cancers. Within each socioeconomic group, black women have a two times higher cervical cancer mortality and a 50% higher breast cancer mortality rate than white women, and black men have a two times higher prostate cancer mortality rate than white men.<sup>105</sup>

Socioeconomic disparities have also reversed over time. In 1950, people in the most-deprived socioeconomic group had a 27% lower cancer mortality rate than those in the most affluent group, but by 2010 to 2014, the most deprived group had a 22% higher cancer mortality than their most affluent counterparts.<sup>105</sup>

Although patients from disadvantaged communities benefit most from health insurance coverage, insurance alone does not overcome the mortality gap. In one study, patients in the poorest communities were more likely to have advanced cancer at diagnosis and less likely to receive cancer-directed surgery than those from the least disadvantaged communities, regardless of health insurance status (this study was funded, in part, by a grant from the NIH/NCI).<sup>106</sup> Another analysis demonstrated that among people with no health insurance, black patients had rates of cancer mortality that were similar to those of white patients, but had higher mortality rates among either Medicaid or private insurance groups.<sup>107</sup>

Even with access to health care, patients may not seek care for many reasons that include having insurance but no health care available nearby, not knowing how to access the health care system, or lack of trust in the health care system.

Other research suggests that socioeconomic disparities in cancer death rates may, in part, be a result of modifiable behaviors that increase the risk of cancer. The 2015 National Health Index Survey showed that prevalence of smoking, obesity, physical inactivity, and inadequate intake of fruit and vegetables was higher

among people with lower education and income levels, and rates of cancer screening were lower.

Taken together, this body of research suggests that addressing cancer disparities and achieving equity calls for multifaceted approaches that are focused on efforts to improve prevention, screening, and access to high-quality cancer care.

### A Policy Focus: Addressing Health Disparities in Cancer Care

Significant cancer health disparities continue to exist in certain populations. Race, ethnicity, socioeconomic status, and geography all affect patient health outcomes, and racial and ethnic minorities and individuals of lower socioeconomic status experience worse cancer outcomes.

To address this issue, ASCO, with the American Association for Cancer Research, the American Cancer Society, and the NCI, released a joint statement to foster cooperation across the cancer research community to ensure that all patients, regardless of demographics, socioeconomic status, or the communities in which they live, benefit from cancer research (the statement was published in *Journal of Clinical Oncology*).<sup>108</sup>

The statement called for defining and improving data measures and tools for cancer disparities research, addressing disparities in cancer incidence, addressing cancer survival disparities, improving community engagement in cancer research, and redesigning clinical trials to acknowledge and address cancer disparities.



## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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## AUTHOR CONTRIBUTIONS

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

## Clinical Cancer Advances 2018: Annual Report on Progress Against Cancer From the American Society Of Clinical Oncology

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## Appendix

Table A1. Additional Notable Advances (October 2016 to October 2017)

Area of Research	Study Title	Reference
Screening	Analysis of plasma Epstein-Barr virus DNA to screen for nasopharyngeal cancer	Chan KCA, et al: N Engl J Med 377:513-522, 2017
Treatment	Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia	Kantarjian H, et al: N Engl J Med 376:836-847, 2017
	Pomalidomide for symptomatic Kaposi's sarcoma in people with and without HIV infection: A phase I/II study	Polizzotto MN, et al: J Clin Oncol 34:4125-4131, 2016
	Phase Ia and Ib studies of the novel carcinoembryonic antigen (CEA) T-cell bispecific (CEA CD3 TCB) antibody as a single agent and in combination with atezolizumab: Preliminary efficacy and safety in patients with metastatic colorectal cancer (mCRC)	Tabernero J, et al: J Clin Oncol 35, 2017 (suppl; abstr 3002)
	Efficacy and safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with melanoma (MEL) metastatic to the brain: Results of the phase II study CheckMate 204	Tawbi HAH, et al: J Clin Oncol 35, 2017 (suppl; abstr 9507)
	Adjuvant capecitabine for breast cancer after preoperative chemotherapy	Masuda N, et al: N Engl J Med 376:2147-2159, 2017
	Irinotecan-temozolomide with temsirolimus or dinutuximab in children with refractory or relapsed neuroblastoma (COG ANBL1221): An open-label, randomized, phase 2 trial	Mody R, et al: Lancet Oncol 18:946-57, 2017
	Hormonal maintenance therapy for women with low-grade serous cancer of the ovary or peritoneum	Gershenson DM, et al: J Clin Oncol 35:1103-1111, 2017
	A phase I study of convection enhanced delivery (CED) of 124I-8H9 radio-labeled monoclonal antibody in children with diffuse intrinsic pontine glioma (DIPG)	Souweidane MM, et al: J Clin Oncol 35, 2017 (suppl; abstr 2010)
	Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation	Stone RM, et al: N Engl J Med 377:454-464, 2017
	Phase III randomized trial of chemotherapy with or without bevacizumab (B) in patients (pts) with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN): Survival analysis of E1305, an ECOG-ACRIN Cancer Research Group trial	Argiris A, et al: J Clin Oncol 35, 2017 (suppl; abstr 6000)
	Efficacy of dabrafenib (D) and trametinib (T) in patients (pts) with BRAF V600E-mutated anaplastic thyroid cancer (ATC)	Subbiah V, et al: J Clin Oncol 35, 2017 (suppl; abstr 6023)
	MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR <sup>+</sup> /HER2 <sup>-</sup> advanced breast cancer who had progressed while receiving endocrine therapy	Sledge GW, et al: J Clin Oncol 35:2875-2884, 2017
Patient care	The impact of exercise on cancer mortality, recurrence, and treatment-related adverse effects	Cornie P, et al: Epidemiol Rev 39:71-92, 2017
	Traveling to a high-volume center is associated with improved survival for patients with esophageal cancer	Speicher PJ, et al: Ann Surg 265.4:743, 2017
	Temporal trends in treatment and subsequent neoplasm risk among 5-year survivors of childhood cancer, 1970-2015	Turcotte LM, et al: JAMA 317:814-824, 2017
	Measuring financial toxicity as a clinically relevant patient-reported outcome: The validation of the Comprehensive Score for financial Toxicity (COST)	De Souza JA, et al: Cancer 123:476-484, 2017
	Long-term results of a phase II randomized controlled trial (RCT) of a psychological intervention (Conquer Fear) to reduce clinical levels of fear of cancer recurrence in breast, colorectal, and melanoma cancer survivors	Beit JM, et al: J Clin Oncol 35, 2017 (suppl; abstr LBA10000)
Tumor biology	Novel molecular subgroups for clinical classification and outcome prediction in childhood medulloblastoma: A cohort study	Schwalbe EC, et al: Lancet Oncol 18:958-971, 2017
	DNA methylation heterogeneity defines a disease spectrum in Ewing sarcoma	Sheffield NC, et al: Nat Med 23:386-395, 2017

Abbreviations: ACRIN, American College of Radiology Imaging Network; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.



## Tumor treating fields: a novel treatment modality and its use in brain tumors

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Tumor treating fields (TTFields) are low-intensity electric fields alternating at an intermediate frequency (200 kHz), which have been demonstrated to block cell division and interfere with organelle assembly. This novel treatment modality has shown promise in a variety of tumor types. It has been evaluated in randomized phase 3 trials in glioblastoma (GBM) and demonstrated to prolong progression-free survival (PFS) and overall survival (OS) when administered together with standard maintenance temozolomide (TMZ) chemotherapy in patients with newly diagnosed GBM. TTFields are continuously delivered by 4 transducer arrays consisting each of 9 insulated electrodes that are placed on the patient's shaved scalp and connected to a portable device. Here we summarize the preclinical data and mechanism of action, the available clinical data, and further outlook of this treatment modality in brain tumors and other cancer indications.

### Preclinical Data and Mechanism of Action

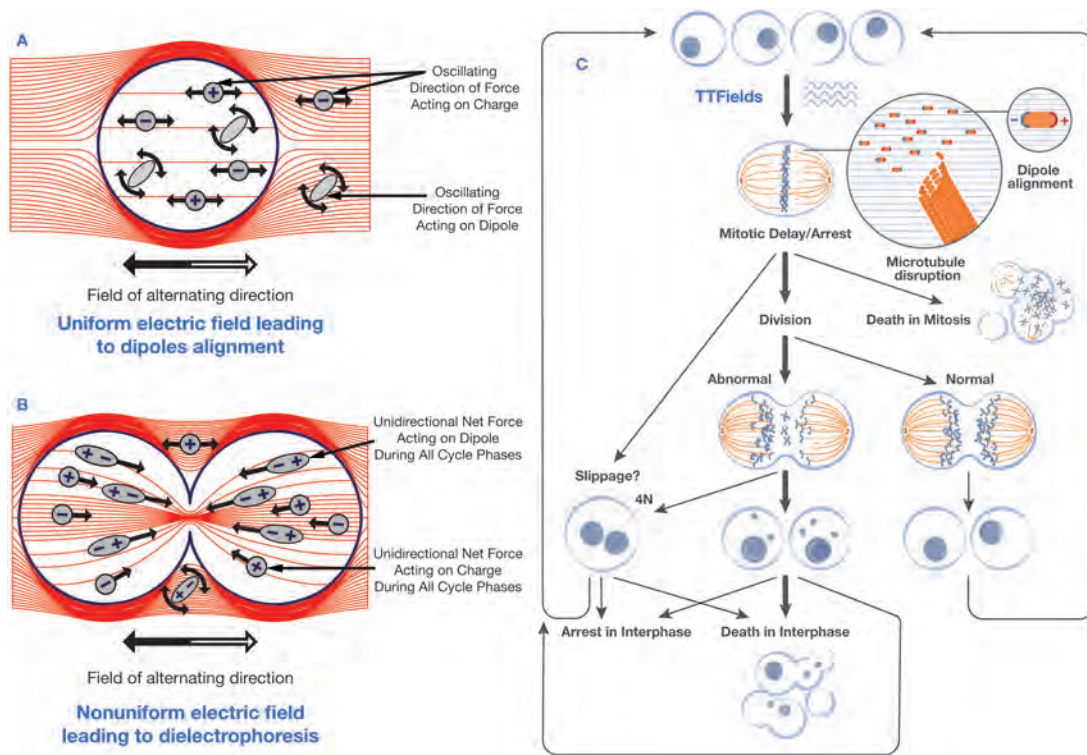
Living cells consist of charged or polar molecules and ions and thus are responsive to electrical fields and currents. Electric activity of cells plays a key role in many essential biological processes including cell division. Cellular processes can be influenced by electric fields. The overall effect will depend upon the magnitude of the potential difference between the 2 electrodes (field intensity) and the frequency: at very low frequencies (<1 kHz) excitable cells such as neurons or myocytes will be depolarized.<sup>1</sup> Cardiac pacemakers or deep brain stimulators work in this range of frequency. At very high frequencies (>MHz), heat is generated in the tissues due to dielectric loss. This property is mainly used for radiofrequency ablation or diathermy treatments.<sup>2</sup> The alternating frequency of electrical fields at intermediate frequencies (range, 10–1000 kHz) is too fast to induce cell depolarization and induces no or only minimal heat by dielectric loss. In the past, these frequencies were considered to have no interaction with biological processes.<sup>3</sup> Nevertheless, a number of effects have been observed in biological tissues such as microscopic particle alignment,<sup>4</sup> cell rotation,<sup>5</sup> and transient pore formation in cell membranes.<sup>6</sup> At low intensities (2V/cm) and intermediate alternating frequencies (between 100–300 kHz), Kirson and Palti et al. demonstrated a specific inhibiting effect on cell division in cancer cell culture models.<sup>7</sup>

Tumor treating fields (TTFields) are alternating, low-intensity, intermediate frequency electric fields that aim to disrupt cell division and inhibit tumor growth. In initial experiments, exposure of a variety of tumor cell lines to TTFields was shown to exert a profound growth inhibitory effect by inducing cell cycle arrest and apoptosis, while no effect was induced on non-dividing cells.<sup>7</sup> These in vitro observations could also be confirmed in vivo in mice and rabbit tumor models.<sup>8</sup> Further studies demonstrated that the growth inhibitory effect is largely mediated by interference on the mitotic spindle apparatus. TTFields will target proteins with large dipole moments (ie, septins and the spindle microtubules, components essential in the metaphase and anaphase stages of the mitotic cycle for separation and equal distribution of chromosomes).<sup>9,10</sup> Furthermore, inhibition of the polymerization of microtubules interferes with proper assembly of the mitotic spindle apparatus. In telophase, during cytokinesis the hourglass shape taken by the daughter cells that are about to separate induces a nonuniform electric field that is strongly enhanced at the level of the furrow region (→ [fig. 1](#)). This results in dielectrophoretic forces that may attract charged molecules from the cytosol and compromise normal cytokinesis.<sup>7</sup> The antitumoral effect results from disruption of the microtubular assembly during mitosis, blocking formation of the mitotic spindle apparatus and blocking separation of the 2 daughter cells.<sup>9</sup> This effect also results in abnormal chromosomal segregation and reduced clonogenic potential of the cell's progeny.<sup>10</sup>

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**Fig. 1.** Mechanisms of action of tumor treating fields in and around quiescent and dividing cells. Inside quiescent cells (1A), the field is uniform, and the oscillating electric forces result only in “vibration” of ions and dipoles (the forces associated with each half cycle are denoted with white and gray arrows). In contrast, the nonuniform field within dividing cells (1B) induces forces pushing all dipoles toward the furrow. [reprinted with permission from ref. 12] 1C: Tumor treating fields (TTFields) exert directional forces and result in abnormal spindle formation and subsequent mitotic arrest or delay, possibly due to improper attachment of chromosomes to the spindle fibers. Cells can die in mitotic arrest or progress to cell division leading to abnormal aneuploid progeny (highlighted by bold arrow). Abnormal daughter cells die in the subsequent interphase, undergo a permanent arrest or proliferate through additional mitosis where they will be subjected to further TTFields assault. [adapted with permission, refs. 11 and 12]

Animal models of various tumors, including glioblastoma (GBM), non-small cell lung cancer, pancreatic cancer, and malignant melanoma confirmed the inhibition of tumor growth or metastatic seeding when externally applied TTFields were delivered at the appropriate frequencies.<sup>11</sup> As an example, an experimental model of rats with intracranially inoculated GBM cells treated with TTFields at a frequency of 200 kHz over 6 days showed smaller tumors compared with untreated rats.<sup>12</sup> The inhibitory effect was significantly increased when 2 or more, rather than 1 field directions were used.<sup>12</sup> Importantly, synergistic antitumor activity was demonstrated when TTFields were applied in conjunction with cytotoxic chemotherapy with paclitaxel, doxorubicin, cyclophosphamide, or dacarbazine (DTIC).<sup>13</sup>

In summary, TTFields will block the mitotic cell cycle, in particular during metaphase, anaphase, and telophase. This will result in cell cycle arrest or delay in cell division and interfere with organelle assembly, particularly the spindle apparatus (fig. 1 C). The consequences are inadequate cell division and unequal chromosome distribution. Ultimately, cells will die in apoptosis. In order to have an optimal treatment effect, the field intensity and frequency needs to be adapted to the tumor type and cell properties (eg, cell size). The optimal frequency to maximize the antitumor effect is inversely

correlated with cell size and when the incident angle of the electrical field is perpendicular to the mitotic plate.<sup>7</sup>

As the cell division may occur at any time, prolonged exposure to the electrical fields is required for maximal effect. For the delivery of TTFields, a portable and battery-powered device has been developed (→ fig. 2). The electric field is applied to the brain through 4 transducer arrays with 9 insulated electrodes each and continuous temperature sensing fixed to the patient's shaved scalp.

## Clinical Experience:

### *Glioblastoma as a Proof of Concept Model*

In the very first clinical application, TTFields treatment was applied to patients with cutaneous metastases of melanoma or breast cancer. Tumor shrinkage or even complete disappearance was demonstrated.<sup>12,14</sup> However, metastatic cancer is a systemic disease, thus most effects of application of TTFields would be expected to be seen in diseases or situations where primarily locoregional control is warranted. Primary brain tumors—and notably glioma—rarely metastasize; recurrence in the brain is the predominant cause of treatment failure and was chosen as the first disease in which the effect of TTFields could be investigated prospectively.





**Fig. 2.** Tumor treating fields (TTFields) device (2nd generation Optune) and its clinical use TTFields are administered by 4 transducer arrays placed on the shaved scalp and connected to a portable device generating 200 kHz electric fields within the brain. The position of the transducer arrays are determined by the localization of the tumor using a mapping software (NovoTal™). (Photo with permission from the patient)

In a computational model, the optimal frequency of TTFields for GBM was found to be in the range of 200 kHz. The field strength should be  $\geq 1$  V/cm. These TTFields are able to penetrate into the deep brain tissue from the surface of the scalp. The computational model also revealed inhomogeneous fields with intensification of the field strength near the ventricles as a result of the high conductivity of the cerebrospinal fluid. Necrotic areas and edematous regions also showed high conductivity of the TTFields. In contrast, areas with high cellularity showed lower conductivity.<sup>15</sup>

Following the demonstration of feasibility in a small pilot trial, the clinical merits of this innovative cancer treatment were evaluated in 2 pivotal randomized trials in recurrent (EF-11) and newly diagnosed (EF-14) GBM. In our summary, herein we always refer to the results of the intent-to-treat population (ITT); for details on the predefined per protocol populations, the reader is kindly directed to the respective original publications<sup>16,17</sup> (→ table 1).

## TTFields in Recurrent Glioblastoma

### The EF-11 Trial

For this trial, GBM patients with progressive or recurrent disease after initial treatment with radiotherapy and TMZ chemotherapy were eligible. Patients may have received several lines of prior chemotherapy. A total of 237 patients were then randomized 1:1 to either the novel TTFields therapy (120 patients) or to the best available treatment (117 patients) according to the local oncologist's best choice (active control, fig. 3A). The primary endpoint of the trial was OS. Patients' median age was 54 years, with a median KPS of 80% (range, 50–100%). Eighty-eight percent of patients had received 2 or more lines of prior chemotherapy including prior bevacizumab in 18% of patients. With a median survival of only 6.6 and 6.0 months in the TTFields and the control arm, respectively (hazard ratio: 0.86 [95% CI, 0.66–1.12],  $P=0.27$ ) and a 1-year survival rate of only 20% in both groups, the trial failed to demonstrate superiority over “established” or commonly used chemotherapy



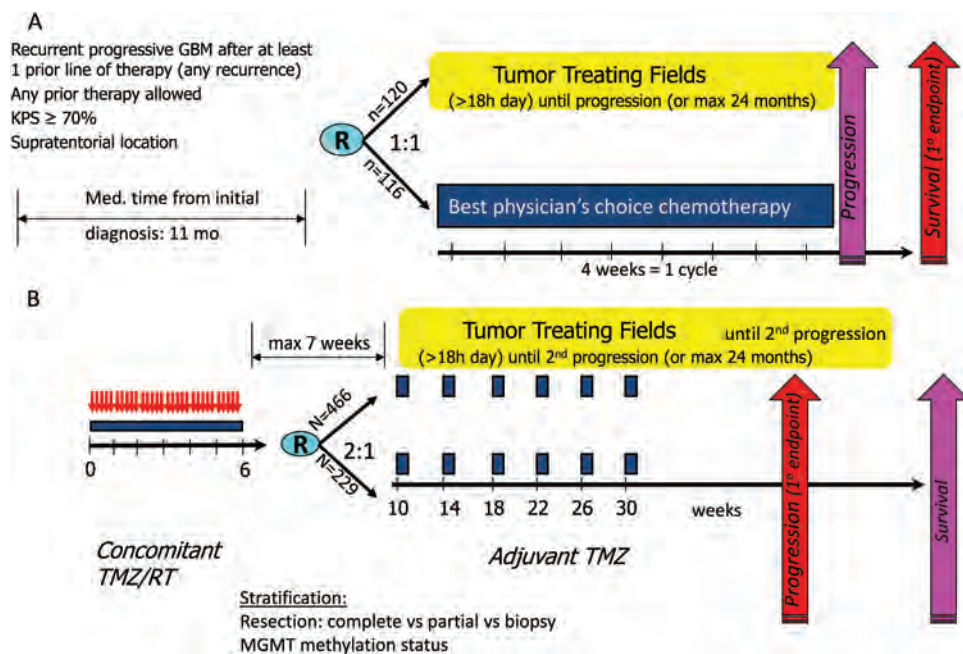
**Table 1.** Results of EF-14 & EF-11 trials

Trial	Treatment arm	Number of patients	Progression-free survival		Overall survival		
			Median	at 6 months	Median	at 1 year	at 2 years
EF-14: newly diagnosed [Interim data set]	TTFields & TMZ	210 (466 total)	7.1 mo*	57%	19.6 mo	75%	43% (36–50)
	Maintenance TMZ	105 (229 total)	4.0 mo*	34%	16.6 mo	69%	29% (21–39)
	Hazard ratio		0.63 (CI, 0.43–0.89)		0.74 (CI, 0.56–0.98)		
	P value		< 0.01 (stat. significant)		0.0004 (stat significant)		
EF-11: recurrent GBM	TTFields	120	2.2 mo.	21%	6.6 mo*	20%	8%
	chemotherapy†	117	2.1 mo.	15%	6.0 mo*	20%	4%
	Hazard ratio		0.81 (CI, 0.60–1.09)		0.86 (0.66–1.22)		
	P value		0.13 (not significant)		0.27 (not significant)		

Abbreviations: CI, 95% confidence interval; mo, months; TMZ, temozolomide; TTFields, Tumor Treating Fields; EF, electrical fields

†: best physician's choice chemotherapy as active control

\*: primary trial endpoint, other values are predefined secondary endpoints

**Fig. 3.** Design of the pivotal trials in GBM. A: EF-11 Trial Design B: EF-14 Trial Design

regimens. The median duration of TTFields administration was only 2.3 months (95% CI, 2.1– 2.4) with tumor progression as the primary reason for discontinuation of treatment. Still it showed objective responses with TTFields alone in 14% of patients compared with 9.6% in the control arm. The study demonstrated safety and feasibility of TTFields in a large multicenter setting.

The design and conduct of the EF-11 trial had some inherent limitations: numerous prior treatment lines were allowed and led to a heterogeneous patient population. More than 40% of patients were included after the third recurrence, including many patients who had failed prior bevacizumab therapy. Thus, most patients suffered from very advanced disease and had only few available treatment options and limited life expectancy. In the absence of a commonly accepted standard treatment for recurrent GBM, the control patients

were to receive the best available systemic therapy according to the current local practice. The heterogeneity of treatments prescribed to the control patients reflects this fact: about one-third of the control patients received bevacizumab alone or in combination, 25% nitrosoureas, and 11% re-exposure to TMZ. A number of patients were discontinued from TTFields therapy very early (after <1 month of therapy), presumably due to absence of a treatment response (rather than true tumor progression) based on skepticism of the investigators. It is known that TTFields take a prolonged period of time until its effects can be clinically demonstrated or that delayed responses may occur after initial radiological tumor growth; thus, some patients may have discontinued TTFields treatment prematurely.

Based on the results of the EF-11 trial, the US Food and Drug Administration (FDA) felt that these results provided reasonable



assurance that the benefits of TTFields outweigh its risks when administered as monotherapy in place of standard medical therapy and therefore approved TTFields in 2011 (<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm251669.htm>).

### *TTFields in Daily Practice: PriDE Dataset*

After FDA approval, TTFields became commercially available in the United States, and Mrugala et al summarized the daily practice experience on 457 patients treated at 91 US institutions (Patient Registry Dataset; PriDe).<sup>18</sup> Interestingly, patients' age and performance status were similar in this dataset and in the EF-11 trial; however, treatment with TTFields was initiated much earlier in the course of the disease. One-third of patients were treated at first recurrence (compared with 9% in the EF11 trial). Overall, median survival was 9.6 months, and the subgroup of patients who were treated at first recurrence (n=152) had a median survival of 20 months.<sup>18</sup>

### *TTFields in Newly Diagnosed GBM (EF-14 Trial)*

This open label phase 3 study in patients with newly diagnosed GBM was initiated while the trial for recurrent disease was still ongoing. For practical reasons (interference of the electrodes during radiotherapy), patients had to be randomized only after completion of standard concomitant TMZ chemoradiotherapy to standard maintenance TMZ chemotherapy (for 6–12 cycles) with or without concomitant administration of TTFields (fig. 3B). The primary endpoint was PFS, and OS was a powered secondary endpoint. Eligible adult patients (KPS  $\geq$  70%, supratentorial tumor location) had to be progression-free after the end of chemoradiotherapy, thus excluding the patients with the worst prognosis. After stratification by extent of resection (biopsy, partial resection, gross total resection, determined on MRI 24–48 hours postsurgery) and MGMT status (methylated, unmethylated, unknown) patients were randomized at a ratio of 2:1 within 3–7 weeks from the last day of radiation. Patients assigned for TTFields therapy received additional instruction and technical support for the use of the device by a device specialist (technician) during the first weeks of treatment and thereafter with monthly visits. This support was limited to technical aspects of the device and assistance with the application of arrays.

A total of 695 patients from 83 centers across the world were included between July 2009 and November 2014. More than half of the patients came from the United States. The medical follow-up was similar in both treatment arms. It included monthly clinic visits for complete physical examination and blood hematology and chemistry analyses. A mini-mental status examination (MMSE), quality of life evaluation (EORTC QLQ-C30 questionnaire and the brain-specific module BN-20) were performed at baseline and every 3 months thereafter.<sup>19,20</sup> MRI and disease assessment using the Macdonald criteria were to be performed every 2 months. All treatment-related clinical decisions were based on local interpretation of imaging; however, a blinded central imaging and disease assessment review determined the date of progression. Patients experiencing tumor progression were offered second-line treatment according to local practices. Patients were allowed to continue TTFields treatment beyond first progression

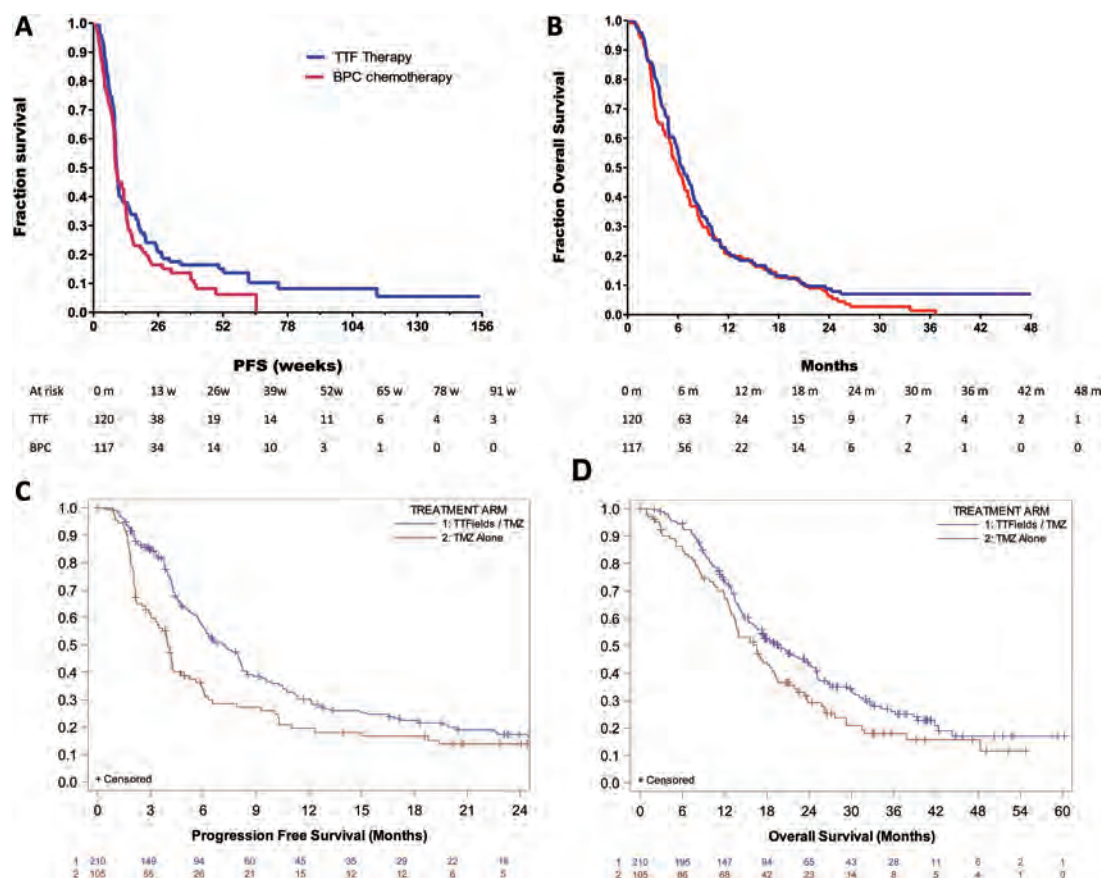
based on the prior experience of pseudoprogression and delayed responses. For the purpose of the trial, the date of first progression, as assessed by the independent review panel, was considered the primary endpoint.

The baseline patient characteristics were well balanced between the 2 groups. In both groups, 66% were male, and the median age at inclusion was 57 years (range, 20–83y), and the median KPS was 90%. Sixty-four percent of patients underwent gross total resection, and 11% had biopsy only. Central MGMT gene promoter methylation analysis was available for 72% of patients. MGMT was methylated in 39% of patients in the TTFields/TMZ group and in 41% of the control TMZ group. The median time from end of radiation therapy to randomization was 36 and 38 days in the TTFields and control groups, respectively. The median time from randomization to initiation of TTFields was 5 days. Median time from diagnosis of GBM to randomization was 3.8 months in both groups (ranges, 2.0–5.7 and 1.4–5.7 months in the treatment and control groups, respectively). Of note, 53% of patients were randomized after initiation of the first cycle of TMZ (as allowed by the protocol). Per protocol, TTFields treatment was continued up to the second progression in two-thirds of the patients; the median duration of treatment with TTFields was 9 months (range, 1–58 mo). Three-quarters of patients receiving treatment with TTFields were adherent to therapy as prescribed (ie, wearing the device  $\geq$  18 hours per day on average during the first 3 treatment months) (n=157/210).

At a prespecified interim and futility analysis to be performed once the first 315 randomized patients reached a minimum follow-up of 18 months, a significant improvement in progression-free and overall survival was seen; consequently the independent data monitoring committee recommended that the trial be terminated early for success and that patients be allowed to cross over to the TTFields arm. In the interim analysis, the ITT median PFS was increased by 3.1 months in the TTFields group with a median PFS of 7.1 months (95% CI, 5.9–8.2 mo) compared with 4.0 months (95% CI, 3.3–5.2 mo) in the control group (HR, 0.62 [98.7% CI, 0.43–0.89];  $P=.001$ ). As a direct consequence, patients in the control group received a median of 4 cycles of TMZ (range, 1–24), whereas patients in the TTFields group received a median of 6 cycles (range, 1–26) of TMZ. Median OS from randomization (ITT) was 19.6 months (95% CI, 16.6–24.4 mo) in the TTFields plus TMZ group compared with 16.6 months (95% CI, 13.6–19.2 mo) in the TMZ control group (HR: 0.74 [95% CI, 0.56–0.98];  $P=.03$ ). The percentage of patients alive at 2 years following enrollment was 43% in the TTFields/TMZ group and 29% in the TMZ alone group ( $P=.006$ )<sup>17</sup> ( $\rightarrow$  fig. 4). At first progression, 67% of the patients in the TTFields/TMZ group received a second-line therapy compared with 57% of patients in the TMZ control group. The type of salvage chemotherapy offered was balanced between the 2 groups: about 40% of second-line therapies included bevacizumab and about 40% nitrosoureas.

Preliminary subgroup analyses showed that the positive effect observed on PFS and OS by the addition of TTFields was not restricted to any subgroup of patients: in particular neither age, performance status, MGMT methylation status nor extent of resection was predictive for a better treatment





**Fig. 4.** Progression-free and overall survival in EF-11 (A&B) & EF-14 (C&D) trials. EF-11 trial: Progression-free survival (A) and overall survival (B) of the intent-to-treat population. Hazard ratio for overall survival: 0.86 (CI, 0.66–1.12,  $P=0.66$ ) [Reprinted with permission from ref, 16] Progression-free survival (C) and overall survival (D) of the intent-to-treat population in the EF-14 trial (interim data set). Hazard ratio for progression 0.63 (95%CI 0.43–0.89,  $P<0.01$ ); for survival 0.74 (CI 0.56–0.98,  $P=0.0004$ ). [Reprinted with permission, ref. 17]

effect. However, the sample size of the interim dataset may not be large enough to identify meaningful subgroups, and detailed subgroup analyses are to be performed on the final and validated dataset. Due to the 2:1 randomization, the control arm comprised only 105 patients, which limited the ability to perform formal subgroup analyses. In the final dataset, the control group will comprise 229 patients. Before publication of the interim analysis, the overall dataset of 695 randomized patients was statistically scrutinized. It was concluded that the results are unlikely to change substantially once the whole dataset reaches a mature follow-up (see supplemental material, reference<sup>17</sup>). In October 2015, the FDA approved TTFields for use in newly diagnosed GBM patients.

### Toxicity, Support, and Quality of Life with TTFields

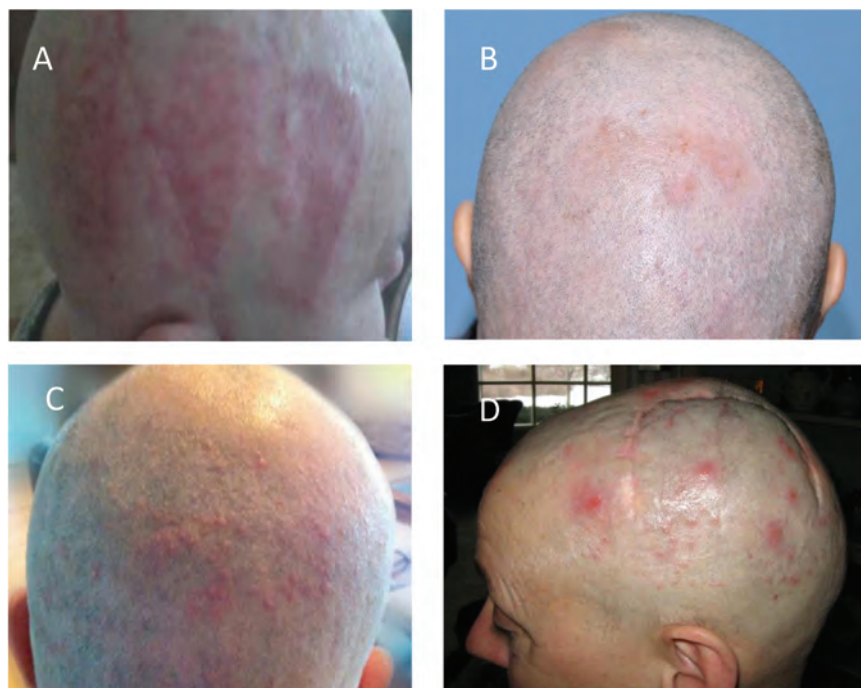
Toxicity related to TTFields therapy consisted, by the nature of this treatment, mainly of local skin irritation. This is usually mild, self-limiting, easily manageable with local application of steroid-containing ointments, and may require an occasional treatment break for a few days. In the EF-11 trial, skin toxicity was reported in 16% of patients (grade 3 in only 2%). In the EF-14 trial for newly diagnosed GBM patients, where the treatment exposure was longer than that for recurrent disease,

grades 1 and 2 skin reactions were reported in 43% of patients. Severe (grade 3) reactions were again seen in only 2% of patients. Examples of allergic contact dermatitis, irritant contact dermatitis, folliculitis, and erosions are shown in → fig. 5.<sup>21</sup>

Importantly, when compared with TMZ maintenance treatment alone, the addition of TTFields did not result in any modification of the overall incidence, severity, and distribution of side effects in patients with newly diagnosed GBM. The incidence of seizures was identical in both treatment groups (7% in the TTFields group vs 8% in the control group). Some nonspecific adverse effects including nervous system disorders such as grade 1–2 headache (21% in the experimental group vs 14% in patients with TMZ alone), mild anxiety, confusion, insomnia, and headaches were reported more frequently in the patients treated with TTFields plus TMZ and occurred mainly at the time of therapy initiation.

Given the need for continuous and long-term use of the TTFields device, the quality of life of patients has been a concern. In the EF-11 trial, there were no differences in global health and social functioning between patients treated with TTFields or chemotherapy. In fact, cognitive and emotional functioning was higher in the TTFields group than in the chemotherapy group.<sup>16</sup> In the EF-14 trial, preliminary quality of life





**Fig. 5.** Skin toxicities observed under tumor treating fields (TTFields). Some mild-moderate (grade 1–2) skin reaction is observed in up to half of patients (in EF-14 trial reported in 43%, grade 3 in 2%); however, it is usually self-limiting and resolves by removing the electrodes for a few days and applying local steroid-containing ointments. The images represent a few examples of skin reactions. (A) allergic contact dermatitis (B) irritant contact dermatitis (C) folliculitis (D), erosions [Reproduced from ref. 21].

data showed identical scores at baseline and at 12 months for patients in the treatment and control groups at the levels of cognitive, emotional, physical, and social functioning.<sup>22</sup> Moreover, the global health status showed an improvement at 3 and 6 months in comparison with baseline for patients treated with TTFields and TMZ, whereas patients in the control group showed a decrease in global health status over the same time period.

## Discussion

More than a decade ago, *in vitro* and *in vivo* experiments in tumor cell lines and in mouse, rat, and rabbit tumor models have demonstrated antitumor activity of low-intensity, intermediate-frequency alternating electric fields. Dividing cells are arrested in metaphase and anaphase, assembly and function of the mitotic spindle are perturbed, and cells ultimately undergo apoptosis. However, in order to translate these findings into a clinically useful treatment, certain conditions must be met: (1) TTFields need to be delivered in a continuous manner to achieve the expected cytotoxic effect; (2) TTFields can only be applied to certain areas of the body, and this (3) requires the possibility to affix transducer array to the skin of the patient over the area of the tumor. As GBM is a disease that remains confined to the CNS and the scalp offers an easy application site for long-term use of transducer arrays, it appeared to be the ideal candidate to serve as a proof of concept demonstration of TTFields.

Two pivotal randomized trials have been reported to date. In recurrent disease, the trial has not demonstrated

improved outcome compared best physicians' choice chemotherapy. However, TTFields when administered as part of the initial treatment in newly diagnosed patients showed a consistent prolongation of both PFS and OS (hazard ratio for death HR: 0.74 (95% CI, 0.56–0.98)). Giving TTFields early in the disease course allows for prolonged exposure, and the *in vitro* observed synergy with TMZ may further enhance its efficacy. The median treatment duration in recurrent disease was only 2.3 months compared with 9 months in newly diagnosed GBM. Still, TTFields alone in recurrent disease have shown objective responses in 14% of patients, consistent or even numerically higher than that observed in other trials using alkylating agent chemotherapy with lomustine<sup>23,24</sup> or TMZ.<sup>25</sup> In the PriDE dataset reflecting routine clinical use of the device, patients who received TTFields at first recurrence were treated for a median of 6.2 months and had a median survival of 20 months, comparing favorably with recent trial results investigating other novel agents. However, a strong selection bias and inclusion of patients with pseudoprogression after initial TMZ chemoradiotherapy cannot be ruled out in this uncontrolled routine practice patient population.<sup>26</sup> The best results with this novel treatment modality have been achieved when TTFields were administered early in the disease course in combination with standard maintenance TMZ therapy,<sup>17</sup> similar to that shown 10 years ago when TMZ was added to standard radiotherapy.

It may be scientifically regrettable that the trial had to be open label and did not include a double-blinded control group. However, a sham device would neither be practically feasible (some heating of the electrodes is inevitable; technically



savvy patients would rapidly figure out whether there is any current flowing), nor acceptable for patients, caregivers, and ethics committees given the perceived burden of shaving the scalp and replacing transducer arrays every 3 days. Whereas some placebo effect might be expected on subjective endpoints, such as quality of life or cognitive function, it is difficult to envision an effect on objective endpoints such as OS or PFS (especially when progression was determined by blinded central radiologists).<sup>27</sup> Requiring a placebo or sham device would also mean a paradigm shift in conducting clinical trials with survival endpoints in oncology. Sham radiation therapy would be required for RT trials, and a placebo control would only be feasible for agents that have rare and mild toxicities.

Indeed, patients receiving TTFields therapy received some additional assistance by the technical support team providing the TTFields device and arrays. However, this support was on average limited to 1 visit per month, and 1–2 extra visits or contacts at the initiation of treatment. Most patients became rapidly independent and self-proficient with the device; on average, there was a median of 1.12 visits per patient and month of treatment (range, 0.5–4 visits per month).

It is highly unlikely that this additional technical support would translate into a 3-month prolongation of median survival, which is in the range of the benefit seen with the introduction of TMZ.<sup>26</sup> In a contemporary randomized open-label non-placebo-controlled trial, patients in the experimental arm received twice weekly i.v. administration of cilengitide. Still, this did not translate into any benefit in outcome (hazard ratio for death: 1.02; 95% CI 0.81–1.29).<sup>28</sup>

It might have been possible that the control arm in EF-14 performed exceptionally poorly. We thus scrutinized the data and compared the performance of the control arms of contemporary trials. The patient characteristics of both the TTFields and control groups were comparable with other clinical trials for newly diagnosed GBM patients in respect to all known prognostic factors (distribution of age, performance status, extent of resection, *MGMT* status).

One important difference in the EF-14 trial compared with many other reports is that patients were randomized only after the end of chemoradiotherapy, and for most patients the first cycle of maintenance TMZ had already been started at time of randomization. This implies that all patients with early tumor progression during the concomitant radiation and TMZ part of the treatment were excluded from this trial. On the other hand, the 3.8 months from diagnosis to randomization will need to be added to survival times in order to have an estimate of the individual patients' effective outcome. The PFS of 4.0 months (from randomization) observed in the control group of the EF14 trial is numerically shorter (likely due to the independent imaging review and assessment of progression) but overall comparable to the observed PFS of 5.5 months observed in the RTOG 0525 trial,<sup>29</sup> a trial that also randomized patients only after completion of the concomitant radiochemotherapy part of treatment. Moreover, in both trials, the OS was identical at 16.6 months for the control groups. It is therefore unlikely that the benefit observed in the treatment group of the EF14 trial can be attributed to patient selection and a poor outcome of patients in the control arm.

For many experts in neuro-oncology who were not involved in the trial, the most important criticism to TTFields was the requirement for patients to wear a device and their presumed stigmatization. Having to shave the scalp is indeed a psychological barrier, although in oncology, for decades we have been using cytotoxic agents that are inducing complete hair loss of all body hair and not only the scalp. In our experience, patients and families rapidly adapt to wearing the device and are able to continue their regular activities including work and even sports. Preliminary analysis of the self-reported quality of life data from the EF14 trial showed identical scores for both groups at baseline and at 12 months for patients in the treatment and control group at the levels of cognitive, emotional, physical, and social functioning.<sup>22</sup> To reduce some of the burden of therapy, a second generation of the TTFields device with a reduction in size and weight by about 50% compared with the device used in the EF-11 and EF-14 devices has been developed.

## Conclusions & Future Perspectives

The results of the randomized phase III EF-14 trial provide level 1 evidence that alternating electric fields are able to positively impact tumor growth and significantly extend survival in GBM. As a logical consequence, TTFields were approved by the FDA for newly diagnosed GBM in October 2015. Nevertheless, numerous questions remain and need to be addressed, both within the EF-14 trial and in future studies; Notably, it will be essential to be able to (1) identify the patients most likely to respond to TTFields therapy, (2) further elucidate the mechanism of action of TTFields, (3) elucidate the mechanisms of resistance to and failure of TTFields therapy, and (4) elucidate the pattern and predictors of response.

In GBM we will need to integrate this novel treatment approach in the current standard of care, and ultimately novel clinical trials will also need to integrate TTFields (at least in the control arm). A pragmatic alternative is to stratify patients for the use of TTFields as part of their standard of care in both the standard and experimental arms.

TTFields is a locoregional treatment, and extending its use to other tumor types and metastatic disease is most promising in clinical situations where locoregional disease control is key for quality of life. The excellent compatibility between TTFields and various chemotherapeutic agents has already been demonstrated, not only in GBM patients in the EF-14 trial but also in lung cancer patients.<sup>30</sup> TTFields may also be synergistic with immune therapy approaches. Senovilla et al showed that cells that cannot undergo mitotic exit show hallmarks of immunogenic cell death where the immune system induces a strong response against the dying cells.<sup>31</sup>

The positive results of the EF-14 demonstrate that neuro-oncology can lead the way to innovation. The results of the EF-14 trial paves the way to investigate the role of alternating electrical fields in other oncologic situations amenable to locoregional treatment such as brain metastases, ovarian carcinoma, mesothelioma, or pancreatic tumors (→ table 2). These trials are currently ongoing. For instance, in pancreatic cancer, TTFields therapy, in addition to gemcitabine resulted in a median PFS of 8.3 months (CI, 3–10.3 mo) in a phase 2 study



**Table 2.** Ongoing clinical trials in solid tumors

Disease, indication	Name of trial	Protocol description	# Pts	Phase	Endpoints	Sponsor	NCT#
<b>Recurrent GBM</b>							
Recurrent GBM	EF-26 (Japan)	Prospective, single arm, multicenter, postapproval study of TTFields in recurrent GBM patients	30	IV	Incidence & severity of treatment-related skin & CNS disorders; secondary: 1-y survival; PFS6mo	Novocure (EF-26) (Japan)	NA (Japan)
Recurrent GBM, bev-naive	Optune™+ bev & hypofractionated stereotactic RT in bev-naive GBM	TTFields + bev + SRT in recurrent GBM	27	I	Safety	U Maryland	NCT01925573
Recurrent GBM, at first relapse	Optune™ with bev & carmustine in treating patients with GBM in first relapse	TTFields+ bev + BCNU	20	II, single arm	Safety, PFS, PFS6, OS	UC Davis	NCT02348255
Recurrent bev-refractory GBM	Multicenter study of TTFields + pulsed bev	TTFields + pulsed bev	25	II, single arm	PFS, QoL questionnaires	Univ of Florida	NCT02663271
Recurrent GBM	Phase 2 study of TTFields, enhanced by genomic analysis to identify a genetic signature for response	TTFields	30	II, pilot	Efficacy, QoL	Washington Univ School of Medicine	NCT01954576
Recurrent GBM	Optune™ with bev in GBM	TTFields + bev	40	II, open label	Safety & Efficacy	Case Comprehensive Cancer Ctr, Cleveland, OH	NCT01894061 Start- June 2013 End- April 2017
Newly diagnosed & recurrent GBM	High Resolution MRI 7 MRS to Evaluate Therapeutic Response to Novo-TTF in Newly & Recurrent GBM	TTFields	10	II	RR, using SOC MRIs	Univ of Penn	NCT02441322
<b>Newly diagnosed GBM</b>							
Newly Diagnosed GBM, unresectable	A Phase II Study of Optune™ in combo with BEV & TMZ in pts with newly diagnosed unresectable GBM	RT + bev, followed by TTFields in combo with bev & TMZ	46	II, single arm	Safety & efficacy	Carolinas Healthcare System	NCT02343549
<b>Low grade gliomas</b>							
Newly diagnosed low grade gliomas	Phase II study of Optune™ ± TMZ in pts with Low-Grade Gliomas	TTFields ± TMZ	42	II, single arm	ORR, Secondary- PFS	UCSD	NCT02507232



**Table 2.** Continued

Disease, indication	Name of trial	Protocol description	# Pts	Phase	Endpoints	Sponsor	NCT#
<b>Meningioma</b> Recurrent Atypical & Anaplastic Meningioma	Pilot Study of Optune™ for Recurrent Atypical & Anaplastic Meningioma	TTFields	21	Pilot	Safety & Efficacy	MSKCC	NCT01892397
<b>Brain metastases</b> NSCLC with 1–5 brain metastases following optimal standard local treatment	COMET	Maintenance TTFields vs supportive care-best SOC alone (after completion of standard local therapy)	60	II, randomized	Time to local/distant progression	Novocure (EF-21) EU	NCT01755624
NSCLC with 1–10 brain metastases	METIS	Radiosurgery ± TTFields	240	III, randomized	Time to first cerebral progression	Novocure (EF-25) Global	Pending FDA IDE approval
<b>Solid tumors</b> Advanced pancreatic adenocarcinoma	PANOVA	+ gem or gem/nab-paclitaxel	40	I/II, 2-cohorts	Safety; feasibility; prelim efficacy	Novocure (EF-20) EU	NCT01971281
Recurrent ovarian carcinoma	INNOVATE	Concomitant with weekly paclitaxel	30	I/II pilot study	Safety, toxicity, feasibility & prelim efficacy	Novocure (EF-22) EU	NCT02244502
Pleural mesothelioma	STELLAR	Pemetrexed & cisplatin or carboplatin + TTFields	80	II, open label	Safety & efficacy (OS)	Novocure (EF-23) EU	NCT02397928
Front-line treatment for advanced NSCLC with squamous histology	LUNAR	combination chemotherapy ± TTFields	300	pivotal open-label randomized	Protocol in preparation	Novocure (EF-24) Global	NA

NCT#: ClinicalTrials.gov Identifier, Novocure; Novocure Ltd, manufacturer of TTFields (Optune™) device  
Abbreviations: BCNU, carmustine; bev, bevacizumab (Avastin®); EU, European Union; GBM, glioblastoma; Gem, gemcitabine; MSKCC, Memorial Sloan-Kettering Cancer Center; nab-paclitaxel; albumin-bound paclitaxel (Abraxane®), NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; EU



on 20 patients. The partial response rate was 30% and another 30% stable disease. The median OS for all patients was promising for this disease at 14.9 months. It was not reached in patients with locally advanced disease, and 8.3 months (CI, 4.3–14.9 mo) for patients with metastatic disease with 1-year survival rates of 86% in locally advanced patients and 40% in patients with metastatic disease<sup>32</sup> If those trials confirm the positive effects observed in GBM patients, a truly new cancer treatment modality has been born and will find multiple useful indications alone or in combination with other established or new treatments.

**Conflict of Interest Statement.** The authors declare no conflict of interest relevant to this review article.

**Advisory details:** Roger Stupp has served as the coordinating principal investigator on Novocure-sponsored clinical trials but did not receive any personal or institutional fees from Novocure. **Management details:** Roger Stupp serves as the president of the European Organisation for Research and Treatment of Cancer (EORTC). EORTC conducts academic clinical trials in a variety of tumor types, including brain tumors. The following authors declare paid consulting conflicts as described here: Roger Stupp has served on non-remunerated advisory boards for Novocure Ltd. Andreas Hottinger has served on advisory boards, fees (when applicable) to the institution. Roger Stupp and Andreas Hottinger have received travel support for scientific presentations of the trial results at academic meetings.

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# Post Hoc Analyses of Intention-to-Treat Population in Phase III Comparison of NovoTTF-100A™ System Versus Best Physician's Choice Chemotherapy

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We performed a treatment-based analysis of data from the pivotal phase III trial of the NovoTTF-100A System™ versus best physician's choice (BPC) chemotherapy in patients with recurrent glioblastoma multiforme (GBM), with particular focus on efficacy in patients using NovoTTF Therapy as intended. Median overall survival (OS) was compared for recurrent GBM patients receiving at least one full cycle of treatment with NovoTTF-100A System or BPC chemotherapy (modified intention-to-treat [mITT] population) in the recently reported phase III trial. The relationship between NovoTTF-100A System compliance and OS was evaluated in the ITT population. Kaplan-Meier analyses examined treatment-related differences in OS for various patient subgroups. Median OS was significantly higher in patients receiving  $\geq 1$  course of NovoTTF Therapy versus BPC (7.7 v 5.9 months; hazard ratio, 0.69; 95% confidence interval [CI], 0.52–0.91;  $P = .0093$ ). Median OS was also significantly higher in patients receiving NovoTTF Therapy with a maximal monthly compliance rate  $\geq 75\%$  ( $\geq 18$  hours daily) versus those with a  $< 75\%$  compliance rate (7.7 v 4.5 months;  $P = .042$ ), and Kaplan-Meier analysis demonstrated a significant trend for improved median OS with higher compliance ( $P = .039$ ). Additional post hoc analysis showed significantly higher median OS with NovoTTF Therapy than with BPC for patients with prior low-grade glioma, tumor size  $\geq 18$  cm<sup>2</sup>, Karnofsky performance status  $\geq 80$ , and those who had previously failed bevacizumab therapy. When used as intended in mITT patients with recurrent GBM, NovoTTF Therapy provides an OS benefit compared with chemotherapy in patients with recurrent GBM. This contrasts with the equivalent efficacy reported previously based on analysis of all randomized ITT subjects, including many who did not receive a full cycle of treatment. Higher NovoTTF Therapy compliance corresponds with greater survival benefit in the present study.

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Conflicts of interest: Representatives of the study sponsor were involved in the study design, data collection, and data analysis. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication. Dr. Wong is currently conducting laboratory research funded by Novocure.

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**G**lioblastoma multiforme (GBM) is the most common type of primary malignant brain tumor and presents a major challenge to the neuro-oncology community.<sup>1</sup> The overall prognosis is poor with best standard care, with as few as 8%-20% of patients surviving 2 years following diagnosis<sup>2</sup> and less than 5% surviving beyond 5 years.<sup>1</sup> GBM is characterized by infiltrative growth and invariably recurs even with aggressive initial therapy.<sup>3,4</sup> For patients with recurrent GBM, treatment options are limited, and there is no clear standard of care.<sup>3,5</sup> In 2009, bevacizumab received accelerated US Food and Drug Administration (FDA) approval for recurrent GBM based on phase II trials showing good response rates and progression-free survival compared with historical controls.<sup>5-8</sup> However, about 40% to 60% of treated patients with recurrent GBM are unresponsive to bevacizumab, while others experience serious adverse events,<sup>3,5,9</sup> and all



initially responsive patients relapse.<sup>5</sup> Hence, there is a critical need for additional treatments for patients with recurrent GBM.

The NovoTTF-100A System (Novocure Ltd., Haifa, Israel) is a novel antimitotic cancer treatment for recurrent GBM. The NovoTTF-100A System consists of a portable device that delivers alternating low-intensity, intermediate-frequency, tumor-treating electric fields (TTFields) to the patients' brain via noninvasive transducer arrays attached to the scalp.<sup>10</sup> TTFields have been shown to inhibit the growth and induce the death of a wide range of tumor cells in vitro and in animal tumor models.<sup>11,12</sup> More specifically, by disrupting mitotic spindle formation during metaphase-to-anaphase transition and by causing dielectrophoretic movement of charged or polar molecules and organelles during anaphase and telophase, TTFields promote selective destruction of GBM (or other rapidly dividing) cells via mitotic arrest and apoptosis.<sup>13,14</sup> Preclinical studies also suggest that combining TTFields with chemotherapy may enhance chemotherapeutic efficacy without increasing toxicity.<sup>15,16</sup> NovoTTF Therapy approval was based on pivotal phase III trial results.<sup>17</sup> In this trial, NovoTTF Therapy demonstrated equivalent overall survival (OS) as compared to best physician's choice chemotherapy in patients with recurrent GBM, with significantly fewer serious adverse events and significantly better quality of life.<sup>17</sup>

Given the mechanism of action of TTFields—which, unlike drug therapy, does not include a half-life and applies only during use—we hypothesized superior efficacy would be observed with the NovoTTF-100A System in an analysis of the phase III data that focused on the “as-treated” or modified intention-to-treat (mITT) population rather than on the ITT population examined in the original report. The mITT population included all NovoTTF Therapy patients receiving at least one predefined treatment course (28 days), and all chemotherapy patients receiving at least one course of chemotherapy. To evaluate this hypothesis, we performed a post hoc analysis of the pivotal phase III trial data to investigate the impact of at least one full course of NovoTTF Therapy or chemotherapy on OS in patients. We also examined the correlation between NovoTTF Therapy compliance and OS.

In addition, we performed a number of post hoc analyses to compare OS rates in subgroups of patients in the ITT population who were treated with NovoTTF Therapy or chemotherapy. Of particular interest was the subgroup consisting of patients who had previously failed bevacizumab therapy. More generally, there have been recent reports of very extended and ongoing survival of a subset of patients treated with NovoTTF Therapy,<sup>18,19</sup> and the

post hoc analyses here represent an attempt to identify patient- or disease-related characteristics predictive of response to NovoTTF Therapy. A recent post hoc study by Wong and coworkers<sup>20</sup> of the pivotal phase III trial data identified prior low-grade histology and lower cumulative dexamethasone dose as important factors distinguishing NovoTTF Therapy responders from nonresponders among recurrent GBM patients. However, these variables did not distinguish response to chemotherapy, though the overall number of patients in this analysis was low.

## MATERIALS AND METHODS

### Patient Selection and Study Design

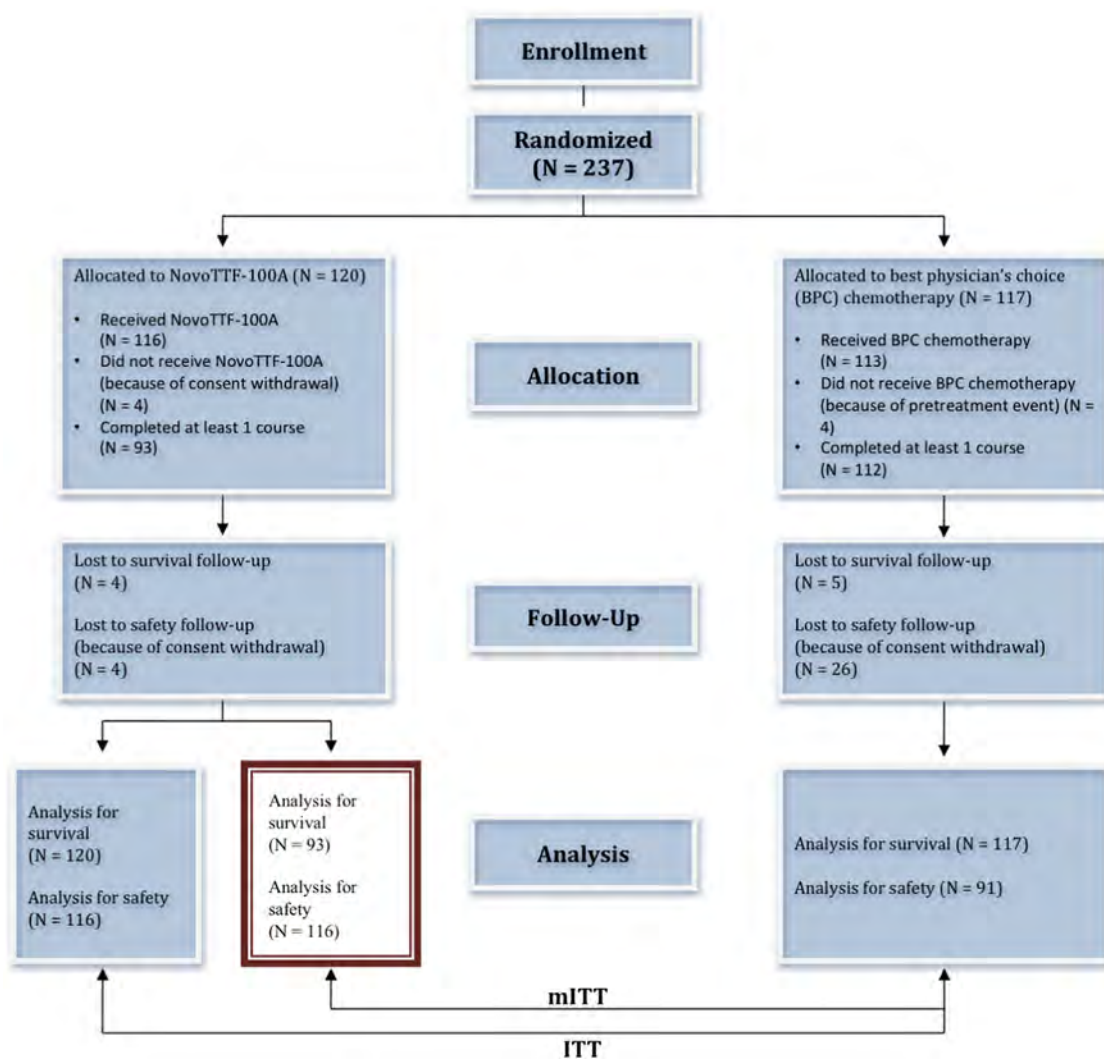
General details of the pivotal phase III trial of the NovoTTF-100A System in recurrent GBM have previously been reported.<sup>17</sup> A CONSORT (Consolidated Standards of Reporting Trials) diagram of the study appears as Figure 1,<sup>20</sup> and includes a breakdown of the respective numbers of patients in the ITT and mITT populations for the survival analysis.

Briefly, between September 2006 and May 2009, adult patients with histologically confirmed and prior treated GBM and radiologically confirmed disease recurrence or progression were randomized in a 1:1 ratio to receive either NovoTTF Therapy (monotherapy) or chemotherapy. Prior therapy had to include radiotherapy, with or without concomitant temozolomide. There was no limit on number or type of prior therapies or recurrences. Patients with an implanted electronic medical device or with an supratentorial tumor location were excluded from enrollment because of a physical limitation: the majority of the electric fields delivered from the transducer arrays on the scalp distributed to the supratentorial part of the brain. For patients assigned to the NovoTTF Therapy group, treatment was self-administered and continuous while they maintained normal daily activity. Patients assigned to the chemotherapy group received a chemotherapy regimen of the local investigator's choice, based on local practice and prior treatment exposure.<sup>17</sup> One cycle of NovoTTF-100A System treatment consisted of continuous treatment for 28 days or 4 weeks, while one cycle of chemotherapy consisted of delivery of the drug until recovery of blood counts or side effects, which usually required 4 to 6 weeks.

### Statistical Analysis

The principal endpoint for the subgroup analyses was OS, computed from the day of randomization until event (death) or censored at the last follow-up according to the Kaplan-Meier method. All survival comparisons between groups were performed using





**Figure 1.** CONSORT (Consolidated Standards of Reporting Trials) flow diagram and modified intention-to-treat (mITT) and ITT populations.

a two-sided log-rank (Mantel-Cox) test with  $\alpha$  of 0.05. Unless otherwise stated, all analyses were performed using the ITT population (all randomized patients regardless of whether they received any treatment). A Cox proportional hazards model (CPHM) was initially used to identify subgroups warranting further evaluation in post hoc analyses. The CPHM used a direct model including all baseline patient and disease characteristics simultaneously. Only characteristics that independently met a  $p$  value of 0.15 or below were considered significant. Based on the results of the CPHM, treatment-related effects on OS were analyzed for the following specific patient subgroups: age ( $\leq 60$  years or  $> 60$  years), Karnofsky performance status (KPS;  $\geq 80$  or  $< 80$ ), surgery status (biopsy only or any resective surgery), GBM type (secondary [prior low-grade glioma] or primary), tumor size ( $\geq 18$  cm<sup>2</sup> or  $< 18$  cm<sup>2</sup>), and bevacizumab failure versus non-bevacizumab failure (prior to enrollment). Treatment-related effects on

OS were also analyzed for reoperation status (yes or no) and maximal compliance ( $\geq 75\%$  or  $< 75\%$  of treatment time [hours/day use]).

Log-rank OS comparisons of the ITT population also were performed for NovoTTF Therapy versus bevacizumab and for NovoTTF Therapy versus chemotherapy (excluding bevacizumab). Differences in OS between NovoTTF Therapy and chemotherapy (including bevacizumab) also were analyzed for the mITT population. The mITT population included all NovoTTF Therapy patients who received at least 1 course of treatment (28 days), and all patients randomized to the chemotherapy group who received at least one course of any chemotherapy protocol, including bevacizumab alone or in combination with cytotoxic chemotherapy.

The relationship between NovoTTF Therapy compliance (calculated as percentage use per day) and mean OS was compared using the Spearman rank correlation coefficient for 40%–59%, 60%–79%, and



80%–100% compliance. The portable device has an internal log file that allows the calculation of patient compliance. Treatment time evaluation was calculated from the first day of a patient's treatment until the last. When a patient did not complete a full 28-day course, the percentage reported was the total number of days treatment was received. This percentage reflected patient compliance with treatment and represented the average daily "dose" of TTFields received. Trend analysis of the relationship between compliance and OS was examined using Kaplan-Meier curves for compliance subgroups and the log-rank test for trend.

## RESULTS

### Patients

The ITT and mITT populations for the NovoTTF Therapy cohort consisted of 120 and 93 patients, respectively, while the ITT and mITT populations of the chemotherapy cohort each contained 117 patients. Baseline characteristics of the ITT population were previously reported.<sup>17</sup> Of note, patient characteristics were balanced for the two treatment groups. Eight percent of patients in both the NovoTTF Therapy group and the active chemotherapy group had a history of prior lower-grade glioma; 21% of NovoTTF Therapy patients and 15% of active chemotherapy patients had a biopsy only; >80% of patients failed two or more prior lines of chemotherapy; and 19% of NovoTTF Therapy patients and 18% of chemotherapy patients failed prior bevacizumab therapy.<sup>17</sup>

### As-Treated (mITT) Analysis of Median OS

Median OS in patients who received at least one course of NovoTTF Therapy was significantly longer

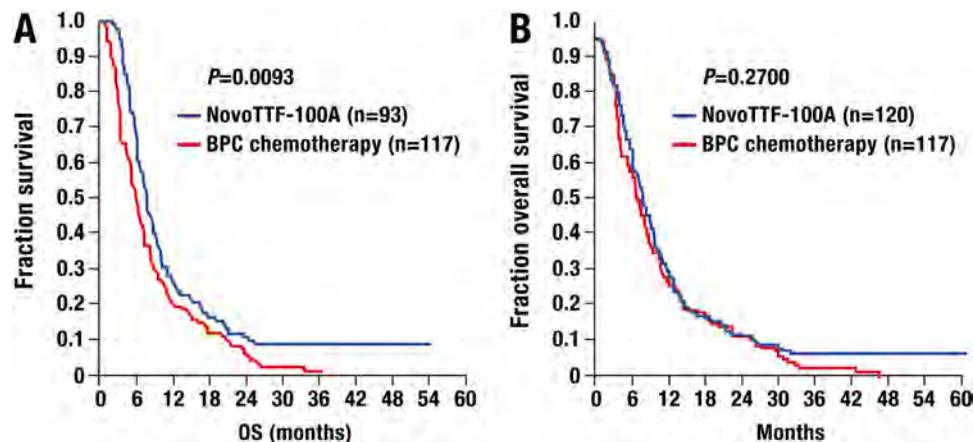
than in patients who received at least one course of any active chemotherapy, including patients who received bevacizumab off-label instead of entering the study (7.8 v 6.0 months, respectively; hazard ratio [HR], 0.69; 95% CI, 0.52–0.92;  $\chi^2 P = .0093$ ). The Kaplan-Meier survival curves are shown in Figure 2.

### Compliance

Ninety-two (77%) of the patients in the ITT population received NovoTTF Therapy  $\geq 75\%$  of the time (median compliance, 86%; range, 41%–98%). Median OS for NovoTTF Therapy patients with a monthly compliance rate  $\geq 75\%$  ( $n = 92$ ) was significantly longer than for patients who received treatment  $< 75\%$  ( $n = 28$ ) of the time, 7.7 v 4.5 months, respectively (log-rank  $P = 0.042$ ). When the NovoTTF Therapy cohort was further subdivided into three groups according to extent of compliance (40%–59%, 60%–79%, or 80%–100% compliance for each 24-hour period), there were 10 (8%), 33 (28%), and 77 (64%) patients in each group, respectively. A Spearman rank correlation test indicated a positive correlation between treatment compliance and mean OS (correlation coefficient, 0.175; one-sided  $P = .030$ ) (Figure 3A). Kaplan-Meier analysis demonstrated a significant trend for improved median OS with higher compliance: median OS of 5.8, 6.0, and 7.7 months for  $< 60\%$  ( $n = 10$ ), 60%–79% ( $n = 33$ ), and 80%–99% ( $n = 77$ ) compliance, respectively (log-rank test for trend,  $\chi^2 P = .039$ ) (Figure 3B).

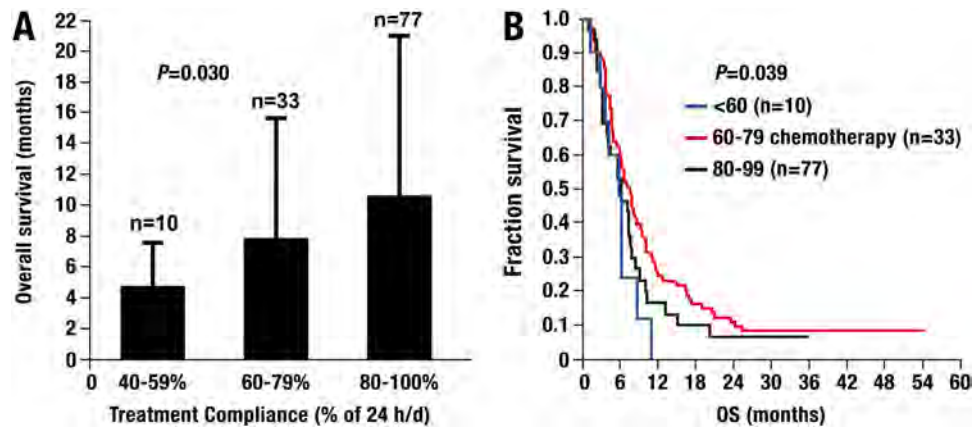
### Subgroup Analyses (ITT population)

Median OS was significantly longer in the NovoTTF Therapy group than in the chemotherapy group for patients who had previously failed bevacizumab, had a prior low-grade glioma, had larger baseline tumor size, and those with higher KPS



**Figure 2.** Kaplan-Meier overall survival for modified intention-to-treat (mITT) (A) and intention-to-treat (ITT) (B) populations with recurrent glioblastoma multiforme treated with NovoTTF Therapy or BPC (best physician's choice) chemotherapy in the phase III trial.





**Figure 3.** (A) Spearman rank correlation between NovoTTF Therapy compliance and mean overall survival (OS) showed a correlation coefficient of 0.175 (1-sided  $P = .030$ ). (B) Kaplan-Meier OS curves stratified according to compliance. There was a trend for longer median OS with better compliance, with median OS of 5.8 months for <60% compliance ( $n = 10$ ), 6.0 months for 60% to 79% compliance ( $n = 33$ ), and 7.7 months for 80% to 99% compliance ( $n = 77$ ) (log-rank test for trend,  $\chi^2 P = .039$ ).

(Table 1). First, among patients who had previously failed bevacizumab prior to enrollment, median OS of those treated with NovoTTF Therapy was 6.0 months ( $n = 23$ ) versus 3.3 months ( $n = 21$ ) for those treated with chemotherapy (HR, 0.43; 95% CI, 0.22–0.85;  $\chi^2 P = .016$ ). Second, for patients who had prior low-grade glioma histology, those treated with NovoTTF Therapy had a median OS of 25.3 months ( $n = 12$ ) versus 7.7 months ( $n = 9$ ) for those who received chemotherapy (HR, 0.31; 95% CI, 0.09–0.99;  $\chi^2 P = .049$ ). Third, for patients who had a baseline tumor size of  $\geq 18 \text{ cm}^2$ , NovoTTF Therapy treatment was associated with a median OS of 5.6 months ( $n = 39$ ) versus 3.3 months ( $n = 41$ ) for those offered chemotherapy (HR, 0.53; 95% CI, 0.32–0.85;  $\chi^2 P = .009$ ). Last, for patients with baseline KPS  $\geq 80$ , subjects treated with NovoTTF Therapy had a median OS of 7.9 months ( $n = 83$ ) versus 6.1 months ( $n = 77$ ) for those treated with chemotherapy (HR, 0.71; 95% CI, 0.51–0.99;  $\chi^2 P = .045$ ) (Figure 4).

Because we observed a significant difference in treatment efficacy between the two trial cohorts who had failed bevacizumab prior to enrollment, we asked whether there is also a difference in efficacy between NovoTTF Therapy and chemotherapy. Indeed, median OS was also significantly longer for patients who received NovoTTF Therapy than for those who received bevacizumab for recurrent GBM in the trial control group, 6.6 months ( $n = 120$ ) versus 4.9 months ( $n = 36$ ), respectively (HR, 0.64; 95% CI, 0.41–0.99;  $\chi^2 P = .045$ ), but not for those who received non-bevacizumab chemotherapy, 6.6 months ( $n = 120$ ) versus 6.6 months ( $n = 84$ ) (HR, 0.92; 95% CI, 0.68–1.24;  $\chi^2 P = .586$ ) (Figure 5). Table 2 provides the baseline characteristics of patients in the NovoTTF Therapy and bevacizumab groups.

Median OS did not significantly differ between NovoTTF Therapy and chemotherapy in the following subgroups (Table 1): non-bevacizumab failures (6.7 and 7.2 months, respectively; HR, 0.95; 95% CI, 0.70–1.27;  $\chi^2 P = .714$ ); patients without prior history of low-grade glioma (6.6 and 5.8 months, respectively; HR, 0.95; 95% CI, 0.72–1.26;  $\chi^2 P = .744$ ); tumor size  $< 18 \text{ cm}^2$  (7.3 and 8.3 months, respectively; HR, 0.99; 95% CI, 0.71–1.37;  $\chi^2 P = .941$ ); KPS  $< 80$  (4.8 and 5.4 months, respectively; HR, 1.26; 95% CI, 0.79–2.02;  $\chi^2 P = .338$ ); age  $\leq 60$  years (7.4 and 6.2 months, respectively; HR, 0.74; 95% CI, 0.54–1.02;  $\chi^2 P = .063$ ); age  $> 60$  years (4.8 and 5.7 months, respectively; HR, 1.31; 95% CI, 0.78–2.19;  $\chi^2 P = .309$ ); patients who received any surgery (6.2 and 6.0 months, respectively; HR, 0.99; 95% CI, 0.74–1.33;  $\chi^2 P = .959$ ); and patients who had biopsy only (7.9 and 5.8 months, respectively; HR, 0.54; 95% CI, 0.27–1.09;  $\chi^2 P = .085$ ). Median OS was also similar in both NovoTTF Therapy and chemotherapy patients who underwent reoperation before randomization (7.4 and 7.4 months, respectively) and in non-reoperated patients (6.3 and 5.3 months respectively).

## DISCUSSION

This analysis demonstrates that NovoTTF Therapy, when used as intended in the mITT population who participated in the phase III trial, is associated with significantly longer median OS than is BPC chemotherapy in patients with recurrent GBM. We found that NovoTTF Therapy was associated with nearly 2 months longer survival (7.8 v 6.0 months) and a roughly 30% reduction in risk of death (HR, 0.69; 95% CI, 0.52–0.92;  $\chi^2 P = .012$ ) when compared to patients treated with BPC chemotherapy.



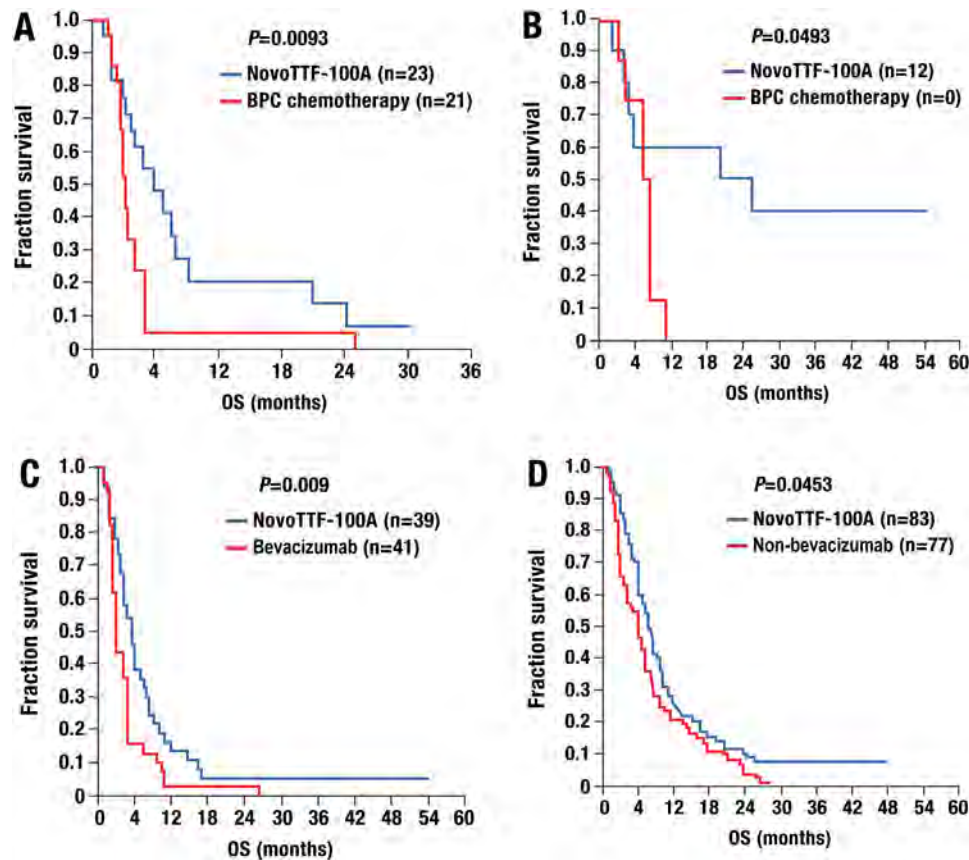
**Table 1.** Subgroup Analyses Showing Overall Survival for NovoTTF Therapy Versus BPC Chemotherapy Patients in the Intention-To-Treat Population

	NovoTTF Therapy	Chemotherapy	Hazard Ratio (95% CI)	Log-Rank P
<b>Prior bevacizumab failure</b>				
Patients, n	23	21	—	—
Median OS, mo	6.0	3.3	0.43 (0.22-0.85)	.0156
<b>Non-bevacizumab failure</b>				
Patients, n	97	96	—	—
Median OS, mo	6.7	7.2	0.95 (0.71-1.27)	.7136
<b>Prior low-grade glioma (secondary recurrent GBM)</b>				
Patients, n	12	9	—	—
Median OS, mo	25.3	7.7	0.31 (0.09-0.99)	.0493
<b>Primary recurrent GBM</b>				
Patients, n	108	108	—	—
Median OS, mo	6.6	5.8	0.95 (0.72-1.26)	.7436
<b>Tumor size <math>\geq 18</math> cm<sup>2</sup></b>				
Patients, n	39	41	—	—
Median OS, mo	5.6	3.3	0.53 (0.32-0.85)	.009
<b>Tumor size <math>&lt; 18</math> cm<sup>2</sup></b>				
Patients, n	81	76	—	—
Median OS, mo	7.3	8.3	0.99 (0.71-1.37)	.9405
<b>Karnofsky performance status <math>\geq 80</math></b>				
Patients, n	83	77	—	—
Median OS, mo	7.9	6.1	0.71 (0.51-0.99)	.0453
<b>Karnofsky performance status <math>&lt; 80</math></b>				
Patients, n	37	40	—	—
Median OS, mo	4.8	5.4	1.26 (0.79-2.02)	.3375
<b>NovoTTF-100A System v bevacizumab (as control group recurrent GBM therapy)</b>				
Patients, n	120	36	—	—
Median OS, mo	6.6	4.9	0.64 (0.41-0.99)	.0450
<b>NovoTTF-100A System v best physician's choice chemotherapy (excluding bevacizumab)</b>				
Patients, n	120	81	—	—
Median OS, mo	6.6	6.6	0.92 (0.69-1.24)	.5860
<b>Age <math>\leq 60</math> years</b>				
Patients, n	85	83	—	—
Median OS, mo	7.4	6.2	0.74 (0.54-1.02)	.0631
<b>Age <math>&gt; 60</math> years</b>				
Patients, n	35	81	—	—
Median OS, mo	4.8	5.7	1.31 (0.78-2.19)	.3087
<b>Biopsy only</b>				
Patients, n	25	18	—	—
Median OS, mo	7.9	5.8	0.54 (0.27-1.09)	.0848
<b>Any surgery</b>				
Patients, n	95	99	—	—
Median OS, mo	6.2	6.0	0.99 (0.74-1.33)	.9590

These data are distinct from the equivalent OS seen in the ITT population.<sup>17</sup> However, the ITT population included all randomized patients, many of whom did not receive a full cycle of NovoTTF Therapy and hence might not have been the best population for testing treatment efficacy against chemotherapy. This is because the anti-tumor effect from alternating electric fields requires continuous treatment and disappears when stopped, while the

biological effects of chemotherapy may persist for 4 to 6 weeks after dosing. The requirement of continuous application of NovoTTF Therapy was tested in prior models of GBM, which suggested that a minimum of four weeks of continuous treatment is required for tumor stasis or shrinkage (see Vymazal et al in this supplement). Consistent with the model data, we included in the mITT analysis patients who received at least one

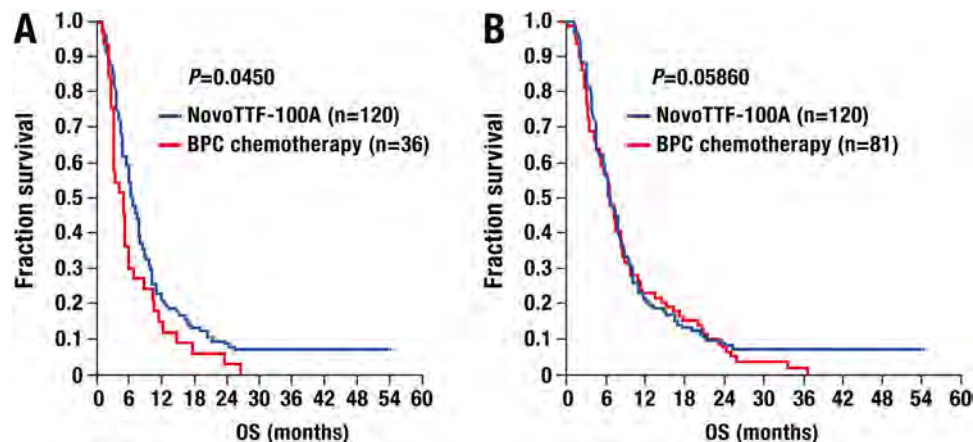




**Figure 4.** Kaplan-Meier overall survival (OS) curves stratified according to patient subgroups in the intention-to-treat (ITT) population with (A) prior bevacizumab failure, (B) prior low-grade glioma, (C) tumor size  $\geq 18$  cm<sup>2</sup>, and (D) Karnofsky performance status  $\geq 80$ . BPC = best physician's choice.

continuous 28-day cycle of NovoTTF Therapy and compared them to patients who received chemotherapy, which varied depending on the specific regimen but always consisted of one treatment cycle, as chemotherapies were administered in an intermittent fashion. Arguably, the mITT analysis

provided a more accurate comparison of the two cohorts because they received similar treatment amounts as intended for the trial. Therefore, while the reported results for the ITT population established similar efficacy between NovoTTF Therapy and chemotherapy in recurrent glioblastoma, the



**Figure 5.** Overall comparison of Kaplan-Meier overall survival (OS) curves for intention-to-treat (ITT) population with recurrent glioblastoma multiforme treated with NovoTTF Therapy (n = 120) versus (A) bevacizumab (n = 36) or (B) non-bevacizumab (n = 81) chemotherapy.



**Table 2.** Baseline Characteristics of Patients in the NovoTTF Therapy and Bevacizumab-Treated Subgroup, Respectively (Intention-to-Treat Population)

Characteristic	NovoTTF Therapy (n = 120)	Bevacizumab (n = 36)
Male sex, n (%)	92 (77)	24 (67)
Median (range) age, y	54 (24-80)	51 (29-72)
Recurrence number, n (%)		
First	11 (9.2)	4 (11.1)
Second	58 (48.3)	18 (50.0)
Third	51 (42.5)	14 (38.9)
Median (range) baseline tumor area, cm <sup>2</sup>	14.5 (0-64.1)	15.3 (0-64.3)
Previous low-grade histology, n (%)	12 (10)	2 (6)
Prior bevacizumab failure, n (%)	23 (19)	4 (11)
Median (range) Karnofsky performance status	80 (50-100)	80 (50-100)
Resection for recurrence, n (%)	33 (27.5)	9 (25)
Median (range) dexamethasone dose per day, mg	4.7 (0-38)	4.7 (0-21)

present results from the mITT population suggest NovoTTF Therapy is associated with a better survival benefit when used as intended.

It should be noted that our mITT comparison is limited by the post hoc nature of the analysis, as well as the major difference between the mechanisms of action of NovoTTF Therapy and of the chemotherapies used in the active control arm of the study. Nevertheless, this post hoc analysis allowed us to estimate the magnitude of the difference in OS between the mITT and ITT cohorts treated with NovoTTF Therapy. This is important because future trials of this device in recurrent GBM will need to take into account the effect of early discontinuation on efficacy outcome by having a larger sample size or a lead-in phase to test patients for device compliance in the first 28 days. Furthermore, removing patients who received <28 days of NovoTTF Therapy may have inadvertently biased the mITT analysis in favor of the device because those who did not complete a full cycle of treatment may have stopped because of clinical deterioration. Patients in the control arm who deteriorated at a similar time point may have already completed a full treatment cycle of their assigned chemotherapy. Therefore, the true survival difference between these two groups may lie between the outcomes of the mITT and ITT analyses.

There appears to be a relationship between NovoTTF Therapy compliance and OS. Patients who had an average monthly treatment compliance of more than 75%, which is 18 hours per day or more, had a median OS of 7.7 months, versus 4.5 months for those patients who were compliant <75% of the time. Median OS also appeared to increase in a stepwise fashion with increasing compliance, from 5.8 months with low compliance (<60%) to 6.0 months with medium compliance

(60%–79%) and 7.7 months with high compliance (80%–99%) (log-rank test for trend,  $P = .038$ ). The progressively higher variability from the low- to high-compliance groups may account for the lower Spearman correlation coefficient, but the differences in OS between these compliance groups are still significant. Consistent with the preclinical data, NovoTTF Therapy exerts its antimitotic effect during the times it is applied, and, unlike chemotherapies, it does not have a half-life associated with its mechanism of action. Therefore, our data support the recommended usage for this device:  $\geq 4$  weeks at an average of  $\geq 18$  hours a day (75% of each 24-hour period) for the total number of days.<sup>21</sup>

It can be argued that patients who were more compliant with NovoTTF Therapy were in a better clinical state, which may in turn independently predict longer survival. However, entry into the trial required a KPS of 70 or greater, and this level of KPS would allow the patient to have independent function and management of the device with a caretaker. Furthermore, Vymazal and Wong (in this supplement) also demonstrated a relationship between compliance and radiologic response, suggesting that the extent of compliance may be viewed as the treatment dose exerted onto the tumor. Together, compliance is probably an independent predictor of longer OS, but future prospective testing in a clinical trial is necessary to confirm this observation.

The present study also included post hoc analyses of various patient subpopulations from the phase III clinical trial. The intent here was to identify patient subgroups in the ITT population who might be more responsive to NovoTTF Therapy than active chemotherapy. In future studies, these subgroups can be more rigorously examined in a prespecified fashion, and with sufficient power, to prospectively detect treatment-related differences. Recent reports of



recurrent GBM patients alive 6 years or more after beginning NovoTTF Therapy highlight the need to better identify the clinical characteristics of patients predictive of a robust response to NovoTTF therapy.<sup>18,19</sup> Furthermore, another recent post hoc analysis of the phase III data found higher proportions of secondary GBM (prior low-grade histology) and low dexamethasone usage in recurrent GBM patients who responded to NovoTTF Therapy than in those who did not.<sup>20</sup> The authors suggested that these as well as other genetic/epigenetic factors might determine response to Novo TTF Therapy. The present study identified a number of variables that need to be confirmed and included in future clinical trials. These variables include prior low-grade glioma (or secondary recurrent GBM), tumor size  $\geq 18$  cm<sup>2</sup>, KPS  $\geq 80$ , and patients who had previously failed bevacizumab therapy. Compared to the rest of the cohort, patients with prior low-grade gliomas, tumor size  $\geq 18$  cm<sup>2</sup>, and KPS  $\geq 80$  may have tumors with slower growth or a location farther away from neurologically functional areas of the brain, allowing sufficient time for NovoTTF Therapy to exert its anti-tumor effect. Those who have failed prior bevacizumab therapy may already have an altered immunologic milieu within the tumor microenvironment, facilitating immunogenic cell death that was induced by NovoTTF Therapy.<sup>22,23</sup> Because our findings are based on univariate analyses of multiple, originally unspecified subgroups, they should be viewed with caution, and as hypothesis-generating rather than definitive conclusions. The limitations of subgroup analyses—especially when multiple parameters are examined post hoc, without a prespecified condition or sufficient power to detect differences between groups—include an increased risk for type I and type 2 errors.<sup>24–26</sup>

Although bevacizumab has been approved as treatment for recurrent GBM, some patients with recurrent GBM are initially unresponsive to bevacizumab, while the rest of initially responsive patients eventually become refractory over time.<sup>3,5</sup> Given this observation, it is worth noting that our analysis of patients who had failed bevacizumab therapy demonstrated a significantly longer OS in patients treated with NovoTTF Therapy than in patients who received chemotherapy, 6.0 months ( $n = 23$ ) and 3.3 months ( $n = 21$ ), respectively. Another analysis, comparing the entire NovoTTF Therapy cohort with patients treated with bevacizumab only in the active control group, showed that OS was significantly longer with NovoTTF Therapy compared to bevacizumab, 6.6 months ( $n = 120$ ) and 4.9 months ( $n = 36$ ), respectively ( $P = .045$ ). It is worth noting that these results are the only published randomized results on the efficacy of bevacizumab compared

head-to-head with another active treatment. Further substantiation of these findings is warranted in a prospectively designed trial.

In summary, treatment options for recurrent GBM are limited, and there is no consensus as to best therapy at time of recurrence.<sup>3,5</sup> The NovoTTF-100A System was recently approved for recurrent GBM based on phase III trial results that showed equivalent efficacy with better toxicity and quality-of-life profiles compared with chemotherapy.<sup>17</sup> Results from the present study suggest that, when used as intended, NovoTTF Therapy provides efficacy superior to that of chemotherapy in a heterogeneous population of patients with recurrent GBM. Post hoc analyses identified subgroups of patients who may be particularly good candidates for NovoTTF Therapy, pending further confirmatory studies.

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# Characterization and Management of Dermatologic Adverse Events With the NovoTTF-100A System, a Novel Anti-mitotic Electric Field Device for the Treatment of Recurrent Glioblastoma

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The NovoTTF-100A System (NovoTTF™ Therapy, Novocure Inc.) is a device that delivers alternating electric fields (TTFields) to tumor cells and interferes with mitosis. It is approved for use as monotherapy for the treatment of recurrent glioblastoma (rGB). TTFields are delivered through insulated transducer arrays applied onto the shaved scalp and connected to a battery-operated field generator. The occurrence of dermatologic adverse events (dAEs) is primarily due to the continuous contact between the array-related components and the scalp for periods of 3–4 days (together with other risk factors). These dAEs may include allergic and irritant dermatitis, mechanical lesions, ulcers, and skin infection. The incidence of dAEs in the phase III trial (n = 116) was 16% (2% grade 2, 0% grade 3/4); the post-marketing surveillance program (n = 570) revealed 156 (21.8%) dAEs with some patients reporting more than one event. Prophylactic strategies for dAEs include proper shaving and cleansing of the scalp and array relocation. Treatment-based strategies are AE-specific and include topical or oral antibiotics, topical corticosteroids, and isolation of affected skin areas from adhesives and pressure. The addition of skin care strategies to the NovoTTF-100A System use will maximize adherence to therapy while maintaining quality of life, all of which contribute to the therapeutic benefit of NovoTTF Therapy in rGB. *Semin Oncol* 41:S1-S14 © 2014 Elsevier Inc. All rights reserved.

## INTRODUCTION AND BACKGROUND

### Glioblastoma

**M**alignant gliomas are a group of primary brain tumors that are heterogeneous, highly invasive, and aggressive.<sup>1,2</sup> Glioblastoma (GB) is

classified by the World Health Organization as a grade IV tumor with a median survival of only 15 months and a 5-year survival rate of less than 10%.<sup>3–6</sup> Despite advances in imaging techniques and multimodal treatment approaches, the overall prognosis of patients with GB is still poor.<sup>7</sup> In patients with

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Conflicts of Interest: Mario E. Lacouture, MD, has been a consultant for Novocure. Mary Elizabeth Davis, RN, MSN, AOCNS, has served on an advisory board for Novocure. Grace Elzinga, RN, has no disclosures to declare. Nicholas Butowski, MD, has served on an advisory board for Novocure. David Tran, MD, PhD, has been a member of a speakers bureau and has served on an advisory board for Novocure. John L. Villano, MD, PhD, has been a member of a speakers bureau and has served on an advisory board for Novocure. Eric T. Wong, MD, FANA, has received a research grant from Novocure. Lucianna DiMeglio, MSN, ANP-BC, AOCN, is a Novocure employee. Angela M. Davies, MD, FRCPC, is a Novocure employee.

The NovoTTF-100A System is approved for the treatment of patients with recurrent GBM. Please refer to the Instructions for Use (IFU) for full prescribing information. Novocure provided financial support to Elsevier with respect to this supplement.

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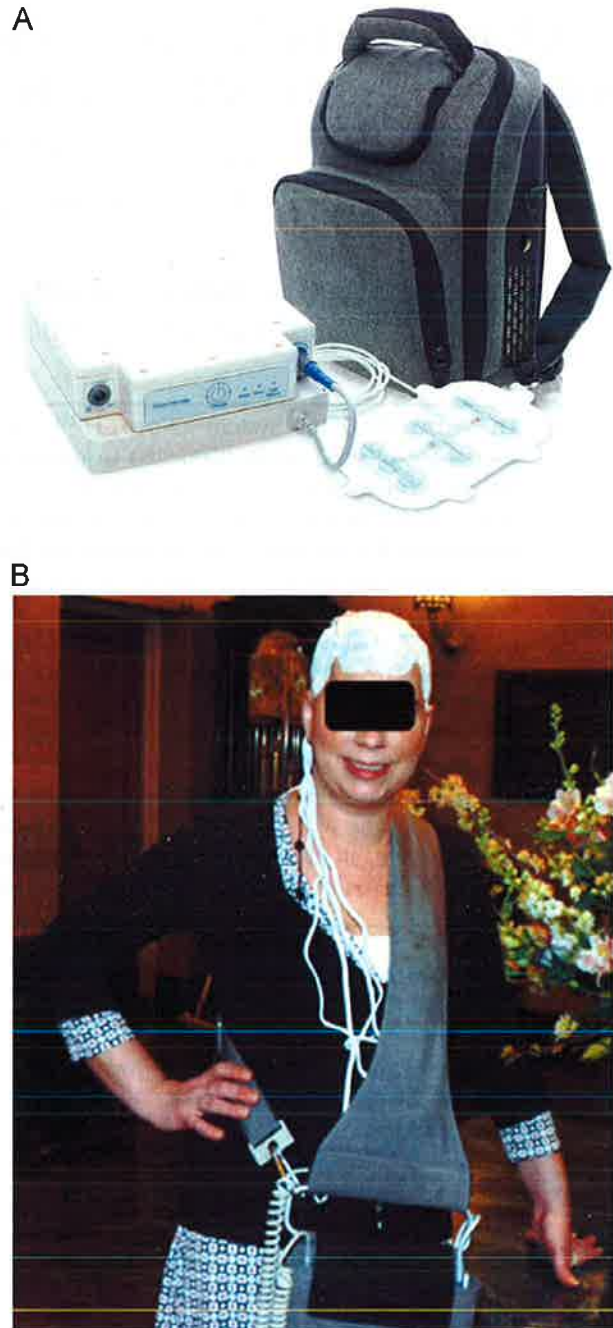
recurrent glioblastoma (rGB), response rates to systemic therapies are typically less than 10%, and the progression-free survival (PFS) at 6 and 12 months are 15% and 6%, respectively.<sup>8</sup> The median overall survival (OS) of these patients with salvage chemotherapy is 5.8 months with a 1-year survival rate of just 21%.<sup>8</sup> rGB patients who are surgical candidates have a median OS of only 4.6 months if left untreated.<sup>9</sup> Furthermore, although treatment with the vascular endothelial growth factor (VEGF) inhibitor, bevacizumab, results in a high radiographic response rate and prolonged PFS, there are no randomized data that demonstrate an increase in OS.<sup>10,11</sup> In fact, recent data have shown that in newly diagnosed GB patients, bevacizumab does not increase OS. Thus, there is a clear need for new and innovative approaches for the treatment of rGB.

### The NovoTTF-100A System

The NovoTTF-100A System (Novocure Inc., Portsmouth, NH) is a novel anti-mitotic device that delivers alternating electric fields (tumor-treating fields, TTFields), and is approved by the US Food and Drug Administration (FDA) and has a European Conformity (CE) mark in Europe for use as monotherapy for the treatment of rGB.<sup>12</sup> The basis of the approvals was a phase III study (EF-11) comparing NovoTTF Therapy to active standard chemotherapy in rGB patients.<sup>13</sup> The NovoTTF-100A System has been commercially available by prescription since 2011 in the United States.

The NovoTTF-100A System consists of four transducer arrays, a connector cable, a field-generating device, and a power source (battery or electrical outlet). Treatment parameters are preset (200 kHz and a minimal field intensity of 0.7 V/cm in the brain); thus, there are no electrical adjustments made by the patient or healthcare provider. TTFields are delivered through non-invasive insulated transducer arrays that are applied to the shaved scalp (Figure 1). The location of the arrays on the scalp is calculated using a simulation software (NovoTAL™, Novocure Inc.) that optimizes the field intensity within a patient's tumor based on head size and tumor location.

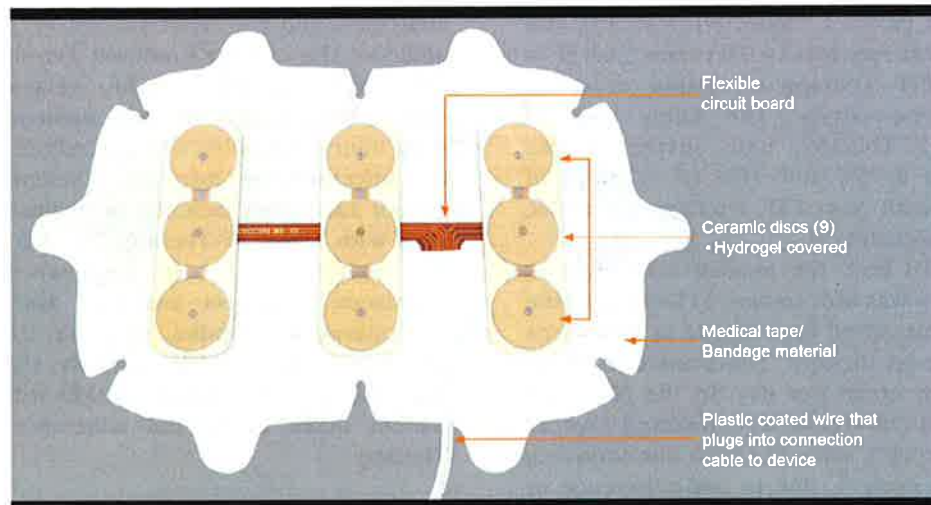
Transducer arrays are supplied to patients in individual sterile packages to minimize the risk of infection, although the application of the arrays to the scalp is not a sterile procedure. The arrays are composed of insulated ceramic discs (nine per array). The ceramic discs (with a high dielectric constant) are biocompatible and are soldered to a flexible circuit board (Figure 2). The ceramic discs do not come into direct contact with the skin as they are separated from the skin by a layer of conductive hydrogel (similar to that found on electrocardiogram



**Figure 1.** The NovoTTF-100A System. (A) NovoTTF-100A System with battery-operated field-generating device, connected transducer array (patient wears 4 arrays), and included backpack for portability. (B) The NovoTTF-100A System as worn during therapy.

pads). There is no direct electron transfer to the skin; ion concentration changes in cells do not occur, nor does electrolysis.<sup>14</sup> The ceramic discs, hydrogel, and circuitry are all attached to a hypoallergenic medical adhesive bandage to keep the arrays in place on the scalp and in continuous direct contact with the skin. A single plastic-coated wire





**Figure 2.** The NovoTTF-100A System Transducer Array.

from each array then plugs into the connection cable, which is attached to the field-generating portion of the device. Although patients have described a "warm sensation" during normal operation of the device, each array has eight temperature sensors (thermistors) that continuously monitor temperature. If the array temperature exceeds 41°C (105.8°F), which is below the threshold for a thermal skin burn,<sup>15</sup> the device will shut off and sound an alarm. The NovoTTF-100A System meets all FDA medical electrical equipment and biocompatibility standards.<sup>16</sup>

NovoTTF-100A Therapy is administered by affixing two pairs of orthogonally positioned transducer arrays to the shaved scalp. Adequate shaving of the scalp is required for optimum array-to-skin contact. The arrays are worn continuously for 3–4 days before removal for hygienic care of the scalp, re-shaving of hair, and reapplication with new sets of arrays.

### Mechanism of Action of the NovoTTF-100A System

While electric fields (at differing frequencies and intensities) have been used in medicine for many decades, it is only within the past decade that the biological effect of alternating electric fields at intermediate frequencies (100–300 kHz), and low intensity (1–3 V/cm), has been realized. Evaluation of these intermediate-frequency, alternating electric fields in multiple cancer cell lines has demonstrated an anti-mitotic effect that is both frequency-specific and intensity-specific in cancer cells, with no effect on non-mitotically active cells.<sup>14,17</sup> TTFs interfere with cancer cell division during three phases of mitosis: (1) metaphase, with inhibition of microtubule spindle assembly; (2) anaphase, with cytoplasmic blebbing and asymmetric chromosomal segregation;

and (3) telophase, with a dielectrophoretic effect, resulting in an inability of the organelles and macromolecules to segregate within the daughter cells due to the formation of a nonuniform field gradient.<sup>18–21</sup> TTFs do not cause cell membrane depolarization and thus do not stimulate nerves or muscles, nor do they cause thermal heating of tissues.<sup>22</sup> The current FDA-approved frequency and intensity settings for the NovoTTF-100A System are optimized for the treatment of rGB.

### Pivotal Phase III Study (EF-11)

A phase III randomized trial (EF-11) was conducted based on encouraging evidence of TTF activity in glioma animal models and subsequent pilot data in patients with newly diagnosed and recurrent glioblastoma demonstrating safety, feasibility, and promising efficacy.<sup>13,14</sup> This trial compared NovoTTF Therapy to active chemotherapy (based on physicians choice) in patients with rGB.<sup>13</sup> Patient characteristics were well balanced between the treatment arms of the trial, median age was 54 years, 19% of patients had previously been treated with bevacizumab, and 90% were at their second or later recurrence. Patients were randomized to NovoTTF Therapy alone (n = 120) or chemotherapy (n = 117), with patients in the active chemotherapy treatment arm receiving either a single agent or a combination containing bevacizumab (31%), irinotecan (31%), nitrosoureas (25%), carboplatin (13%), temozolomide (11%), or other agents (5%).

The primary endpoint of the trial was OS. NovoTTF Therapy demonstrated comparable OS to active chemotherapy, with a median OS of 6.6 versus 6.0 months, respectively (hazard ratio = 0.86 [95% confidence interval [CI], 0.66–1.12]; *P* = .27). The PFS6 (PFS rate at 6 months) was 21.4% versus 15.1%



(hazard ratio 0.81 [95% CI, 0.60-1.09];  $P = .13$ ), and the overall response rate was 14.0% versus 9.6% ( $P = 0.19$ ) for NovoTTF Therapy compared to active chemotherapy, respectively. The safety analyses favored NovoTTF Therapy, with severe adverse events occurring in 6% and 16% ( $P = .022$ ) of patients treated with NovoTTF Therapy and active chemotherapy, respectively.<sup>13</sup>

In the phase III trial, the median adherence to NovoTTF Therapy was 86% (range, 41%–98%) of the time ( $n = 116$ ), measured by a log file in the device that records time on therapy. This translated into a mean use of 20.6 hours per day. In the NovoTTF Therapy group, 93 (78%) patients completed 4 weeks of therapy (one cycle), with 27 (23%) discontinuing treatment within cycle 1, due to non-adherence or inability to handle the device.<sup>13</sup> Adherence with NovoTTF Therapy was the main predictor of improved OS in this trial, with patients who used the device for more than 18 hours a day living significantly longer than those who used it for less than 18 hours a day (7.8 months *v* 4.5 months,  $P < .05$ , respectively).<sup>12</sup> The most common device-related adverse events were grade 1 and 2 dermatologic adverse events (dAEs) of the scalp beneath the arrays, occurring in 18 patients or 16% (all grades; 2% grade 2) and no grade 3 or 4 dAEs. Skin ulceration was observed in one patient (<1%). All dAEs were reversible and did not result in discontinuation of patients from study. Other device-related AEs included headache (3%), malaise (2%), muscle twitching (1%), and fall (1%). Systemic toxicities including grade 3/4 hematologic (17%), gastrointestinal (17%), and infections (8% of patients) were significantly more frequent in chemotherapy-treated patients, compared to 3%, 4%, and 4%, respectively, for patients receiving NovoTTF Therapy ( $P < .05$ ; Fisher exact test).<sup>13</sup>

Quality-of-life was analyzed in patients who remained on therapy for >3 months and for whom quality-of-life data were available ( $n = 63$ , 27%). Whereas no differences in global health and social functioning between NovoTTF Therapy and active chemotherapy were observed, cognitive, social, role, and emotional functioning were all higher in the NovoTTF Therapy-treated group, while their physical functioning was slightly worse when compared to the chemotherapy treatment group. Symptoms that were reported by patients to be more severe with chemotherapy than with NovoTTF Therapy included appetite loss, diarrhea, constipation, nausea/vomiting, pain, and fatigue.<sup>13</sup>

Because the dAEs observed with NovoTTF Therapy are unique to this novel oncologic treatment modality, and treatment continuity is critical for better response to therapy, there is a need for improved nomenclature, preventive and management

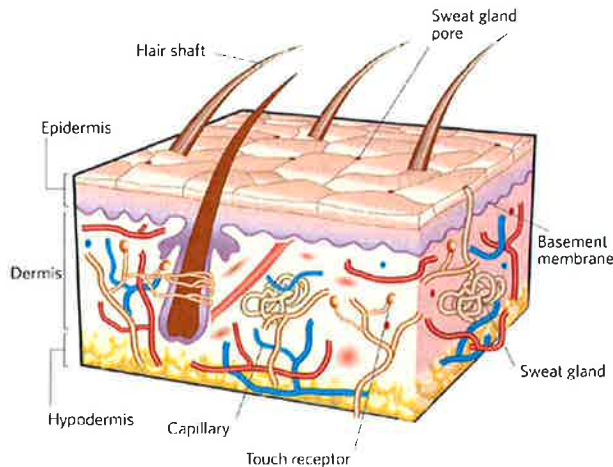
strategies, and the identification of risk factors. In addition, the current Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grading criteria for the skin and subcutaneous tissue disorders; injury, poisoning and procedural complications; and infections and infestations system organ classes do not adequately describe or characterize the dAEs seen with NovoTTF Therapy.<sup>23–25</sup> Efforts to improve the nosology will help communication between healthcare providers and will also improve the description and grading of these dAEs in current and future clinical trials. Similarly, the development of management strategies for dAEs will help maintain patient quality-of-life and adherence to NovoTTF Therapy.

## BASIC PATHOPHYSIOLOGY OF SKIN AND HAIR

In order to understand pathogenic mechanisms underlying dAEs and to develop effective interventions, it is important to recognize that the skin is a complex, mitotically active, multi-layered organ composed of multiple cell types with various functions.<sup>26</sup> Structurally, the skin is composed of three layers: (1) the epidermis, which functions as a permeability and protective barrier and as an organ for immune surveillance; (2) the dermis, which provides the structural support to the skin and contains an extensive lymphatic and neurovascular network; and (3) the hypodermis and the associated subcutaneous fat, both of which provide insulation and contain blood vessels and nerves (Figure 3). All three of these layers function together to form a physical permeability barrier that protects the body from pathogenic microbes and ultraviolet radiation, regulates temperature, allows for the transduction of sensations, repairs wounds, and contributes to an individual's physical appearance and sense of self.<sup>27</sup> Although the epidermis and its outer stratum corneum provide the initial physical barrier to the environment, the structural integrity of skin as a whole is supported primarily by the dermis and hypodermis.<sup>28</sup>

The epidermis is the outermost layer of the skin. It is the only skin layer in direct contact with the hydrogel covering the ceramic discs and the adhesive tape of the bandage holding the transducer arrays in position. The epidermis is a continually renewing structure that gives rise to appendages such as pilosebaceous units (hair follicles), nails, and sweat glands. Epidermal appendages also provide special protective or sensory functions. The epidermis ranges in thickness from 50  $\mu\text{m}$  to 1.5 mm, as compared with the 1.5- to 4.0-mm thickness of the dermis.<sup>29</sup> More than 80% of cells in the epidermis are keratinocytes.





**Figure 3.** Schematic representation of human skin structure and cell population. The skin comprises three main layers: the epidermis, dermis, and hypodermis. The resident cell populations and various structures present throughout the skin allow for maintenance of an efficient barrier against water loss and protection against threats such as ultraviolet radiation (UVR) and microbial pathogens. The blood and lymph vessels allow for the migration of immune cells in and out of the skin, so that the cell population of the skin is constantly in a state of flux, in response to the demands of the cutaneous inflammatory and immune systems. Reprinted by permission from Macmillan Publishers Ltd: Nature (MacNeil S. Progress and opportunities for tissue-engineered skin. *Nature*. 2007;445:874-80), copyright 2007.

In humans, the normal doubling time for keratinocytes is 24 hours, and the transit time for a keratinocyte in the basal layer, from the time it loses contact with the basal layer to the time it enters the stratum corneum (outermost layer in the epidermis), is at least 14 days.<sup>30</sup> Transit through the stratum corneum and subsequent desquamation require another 14 days.<sup>30</sup> Intercalated among the keratinocytes at different levels are other cells—melanocytes, Langerhans cells, and Merkel cells. Additional cells, including lymphocytes, are temporary residents of the epidermis and are rare in normal skin. The innate immune system of the skin, which comprises antigen-presenting cells and circulating immune cells, provides additional antimicrobial functions.

Pathologic changes in the skin exposed to NovoTTF Therapy can occur or become exacerbated as a result of a number of different stimuli. These include repetitive mechanical trauma (as in the application and removal of the arrays<sup>31</sup> or shaving<sup>32</sup>) resulting in erosions, inflammation (from the hydrogel covering the ceramic discs or adhesive<sup>33</sup> or moisture from eccrine sweat or ambient humidity<sup>34</sup>), infection (as in bacterial folliculitis or impetigo<sup>35</sup>), wound healing (surgical scars or delayed healing associated with the use of bevacizumab<sup>36,37</sup>), and

ultraviolet (UV) radiation damage resulting in atrophy and actinic keratoses.<sup>38</sup>

Erosions are moist, circumscribed, depressed lesions that result from loss of a portion or all of the viable epidermis, with mild bleeding and associated with pain or burning.<sup>39</sup> Erosions may result from trauma related to the repeated removal of the arrays or shaving, inflammation and maceration from sweat-derived moisture, rupture of vesicles or bullae from infection, or epidermal necrosis from altered perfusion due to pressure of the arrays. In general, erosions do not result in a scar unless they become secondarily infected.

Dermatitis is a nonspecific term denoting skin inflammation, presenting with edema and erythema, followed by scaling. With NovoTTF Therapy, two types of dermatitis may develop. The first, representing approximately 20% of new cases of contact dermatitis, is allergic contact dermatitis (ACD), a cutaneous inflammatory reaction caused by contact with a specific exogenous allergen to which a person has been sensitized.<sup>40</sup> The second is irritant contact dermatitis (ICD), a nonspecific inflammation of the skin in response to direct chemical damage to epidermal cells and the release of inflammatory chemokines. These two types of dermatitis have unique clinical and pathophysiological characteristics. In ACD, following contact with an allergen (more than 3,700 chemicals have been identified as culprits of ACD<sup>41</sup>), the skin reacts with inflammation and the severity of the dermatitis can range from mild and temporary to severe and persistent. In the latter case, the dermatitis may not resolve unless treated, even if the offending allergen has been withdrawn. When ACD is suspected, allergen identification through epicutaneous patch testing has been demonstrated to improve quality-of-life,<sup>42</sup> as it allows for identification of the condition and avoidance of the causal allergen. In oncology patients, patch testing may not always be feasible due to the frequency of visits necessary (usually four) and concomitant medications that hinder the interpretation of patch testing (ie, corticosteroids, immunosuppressants). In these cases, a provocative use test (PUT) may identify the culprit in some cases.<sup>43</sup>

In ACD, the symptoms will not resolve unless the offending agent is removed and the area is treated with a topical corticosteroid, while ICD will resolve a few days after the culprit is removed. As noted above, ICD is a nonspecific inflammation of the skin manifested by erythema, edema, pruritus or burning, and scaling as a response to direct chemical damage.<sup>44</sup> Thus, in ICD, removal of the culprit is the only treatment necessary.

A more severe dAE is an ulcer, a lesion in which the epidermis and the dermis have been destroyed. Ulcers are usually round and their borders are well



defined. The base of an ulcer may be clean or necrotic and may contain granulation tissue. A discharge is usually indicative of infection and may be purulent, granular, or malodorous. Surrounding skin may be altered. During healing, the ulcer will form a crust composed of dried serum, blood, or exudate. The color of the crust is important: yellow-brown from a dried serous secretion; yellowish-green from a purulent secretion; and reddish-black from a hemorrhagic secretion. Ulcers may result in scarring.

Infections are common in skin and soft tissues given the abundance of microbes present in these structures.<sup>45</sup> A pustule is a circumscribed, raised lesion in the epidermis containing pus. Pus is composed of leukocytes and cellular debris (yellow color) and may contain bacteria (greenish-yellow color) or be sterile (white color). Pustules may contain a hair at the center, may vary in size, and may coalesce to form plaques of pus. Pustules may be confused with vesicles and bullae, which are fluid-filled lesions that are not always infected. Friction vesicles or bullae with clear contents may occur with shear forces on the epidermis or initially with viral infections, whereas those resulting from bacterial infections or late-stage viral infections will have yellow-greenish contents. In cases of bacterial infections resulting in bullae, the term "bullous impetigo" is used.

Scars arise from fibrous tissue proliferations that replace previously normal skin after a wound or ulceration disrupts the integrity of the skin. Surgical scars may retain a deeper pink or red color for months after a surgical procedure, and hairs are usually absent. The blood flow in scars is altered due to excess fibrous tissue deposition, making them susceptible to dAEs with NovoTTF Therapy use when the ceramic discs are placed immediately over them. Similarly, skin scarring, in the form of atrophy and absence of hair follicles, may develop after radiation therapy and may place these areas at higher risk for dAEs.

The use of NovoTTF Therapy involves placement of the transducer arrays directly onto the scalp for at least 18 hours a day. The arrays are left in place for 3–4 days before they are replaced with new arrays that are relocated on the scalp, the latter practice serves to minimize direct contact over the same areas of skin. Prolonged contact with the arrays poses unique chemical, mechanical, moisture, and thermal-related stresses on skin which may account for the development of dAEs. Consequently, continuous application of the transducer arrays without timely exchanges may cause the development of distinct dAEs on the scalp characterized by inflammation and, in some cases, associated with erosions, ulcers, and secondary infections.

The quality of the array-to-scalp contact is negatively affected by hair growth. The scalp contains approximately 100,000 hair follicles. These hair follicles are part

of pilosebaceous units, which contain hair shaft-forming cells, sebaceous glands, and arrector pili muscles. During hair growth, the preceding hair shaft is pushed up and out by a new shaft and results in shedding (normally, approximately 100 strands of hair are shed from the scalp every day).<sup>46</sup> Hair grows approximately 5–12.5 mm every month or 0.2–0.5 mm per day, which results in outward pressure on the adhered transducer arrays and requires repeated shaving at every array replacement (every 3–4 days). This is because an increased distance between the arrays and skin will allow an air gap to form, with air being an insulator for electric fields, and will affect the delivery of TTF fields.

## CHARACTERIZATION OF DERMATOLOGIC ADVERSE EVENTS

In order to characterize the dAEs, data from patients using NovoTTF Therapy were analyzed with a focus on skin-related AEs (including photographs of the scalp reviewed by a dermatologist) from the completed phase III trial (EF-11) of NovoTTF Therapy (n = 116 patients),<sup>13</sup> as well as from those patients with AEs submitted in the post-marketing surveillance program (n = 570 patients). The ongoing phase IV post-approval study in rGB (EF-19; NCT01756729) has not had sufficient enrollment at present to further define dAEs adequately.

Types of dermatologic adverse events were characterized, and associated patient data (if available) were reviewed, including time to development of dAE, clinical presentation, risk factors, and management strategies employed.

In the phase III trial (EF-11) 16% of patients (18 of 116 patients) had grade 1 or 2 dAEs and there was a 1% incidence of skin ulcer (1 of 116 patients). There were no grade 3 or 4 dAEs. Time to dAE onset was 2–6 weeks. These events were graded according to the CTCAE version 3.0. However, this version of the CTCAE did not allow for adequate characterization of the dAEs seen with NovoTTF Therapy. As a result, all dAEs were grouped into the same category.

Although the information available from the post-marketing surveillance program does not allow for detailed grading, 21.8% of patients (156 of 570 patients) had non-serious dAEs, with some patients reporting more than one event. There was a 0.7% incidence of skin ulcer (4 of 570 patients). The median time to dAE onset was 32.5 days (range of 2–520 days). Patients in this setting have reported the need for treatment interruptions or discontinuation of NovoTTF Therapy due to dAEs, but the exact percentage is not known because the post-marketing program is a "self report" program. This latter issue highlights the need for dermatologic management guidelines when NovoTTF Therapy is utilized in



**Table 1. Types and Potential Causes of Dermatologic Adverse Events**

Adverse Event	Potential Cause
Irritant contact dermatitis	Chemical irritation from hydrogel, moisture, and/or alcohol
Allergic contact dermatitis	Allergy to tape and/or hydrogel
Erosion	Mechanical trauma from shaving and/or array pressure/removal
Ulcer	Decreased perfusion from array pressure (especially in areas overlying scars/hardware/prior radiation)
Skin infection/pustules	Secondary bacterial infection

clinical practice outside of the carefully managed setting of a clinical trial.

A review of scalp photographs from patients on the EF-11 trial and from the post-marketing program (when available) by a dermatologist (M.E.L) allowed for the characterization of these dAEs. The clinical presentation of dAEs associated with NovoTTF Therapy can be divided into four major categories: dermatitis (allergic or irritant), erosion, infection, and ulcer (Table 1 and Figures 4–7).

In addition to the above findings, a review of patient data identified the following risk factors that may be associated with NovoTTF Therapy dAEs: (1) placement of ceramic disc(s) from the transducer arrays on the scalp overlying scars or craniotomy hardware; (2) history of contact dermatitis to materials used in the composition of array skin contact materials (ie, tape adhesive or hydrogel); (3) hyperhidrosis (excessive sweating) from hot, humid weather, fever, or occlusive wigs; (4) previous skin exposure to UV or ionizing radiation; (5) high doses or recent change in systemic corticosteroids; or (6) concurrent administration of systemic anticancer agent (eg, chemotherapeutics, biologics, or targeted therapeutics).

## MANAGEMENT OF DERMATOLOGIC ADVERSE EVENTS

The management of the dAEs associated with NovoTTF Therapy can be divided into prophylactic and treatment interventions.

### Prophylactic Interventions

Based on the clinical trial and post-marketing experience to date with NovoTTF Therapy, prophylactic interventions that decrease the risk of dAEs are divided into five categories: (1) patient and caregiver

A



B



**Figure 4.** Contact dermatitis (may or may not be symptomatic). (A) Erythema from scalp irritation that was caused by the adhesive tapes or hydrogel. The allergic dermatitis resolved with the application of a topical corticosteroid. (60-year-old man who had been on temozolomide and NovoTTF Therapy for 7 months). (B) Irritant reaction on the right side of scalp with erythema corresponding to the three strips of hydrogel on the transducer arrays. This adverse event occurred during the hottest days in the summer and was a result of a combination of high ambient temperature, increased humidity, excessive sweating, and patient sleeping on the right side of her head. Treatment required 1-2 weeks of device interruption and use of a topical corticosteroid (65-year-old woman who had been on NovoTTF Therapy for 2 months).

education, (2) scalp preparation, (3) infection prevention, (4) avoidance of scars and craniotomy hardware, and (5) array relocation. Table 2 provides a summary of these practices for use by the patient or caregiver.

### Patient and Caregiver Education

**Scalp preparation.** This basic step is critical to ensure good array-to-scalp contact, which will lower the risk of skin irritation and optimize delivery of the TTFields. Factors that are known to affect array-to-scalp contact include hair length (determined by proper and





**Figure 5.** Dermatologic erosions and skin infection (folliculitis) in a 60-year-old man who had been on temozolomide and NovoTTF Therapy for 3 months.

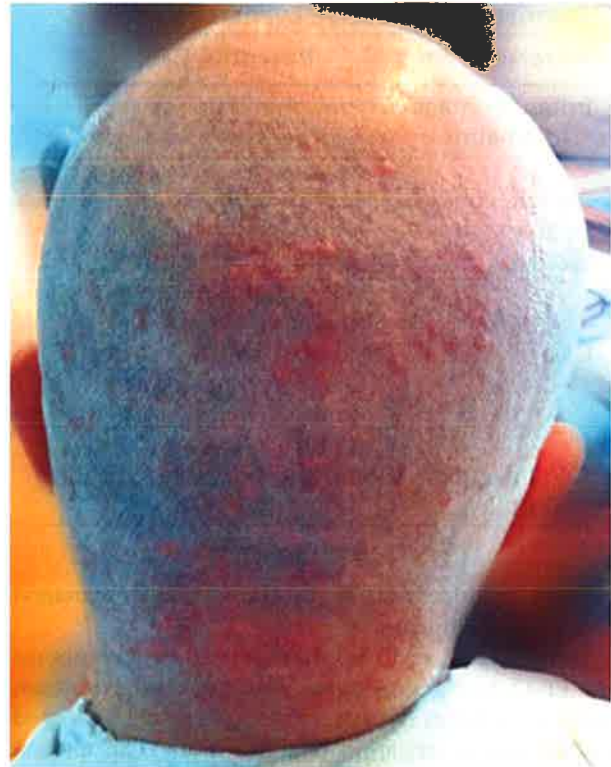
timely shaving), moisture from sweat (determined by eccrine sweating on the scalp), the presence of sebum or the degree of "oiliness" of the scalp (determined by individual patient skin characteristics and removal prior to array placement), and the duration of skin contact with the same set of arrays.

For removing hair from the scalp, an electric razor is recommended because it offers a smaller risk of cuts as compared to a straight blade razor. However, in some patients, the use of an electric razor may actually lead to an increase in folliculitis due to the pulling and tension exerted on the hair while it is being cut. If this is the case, patients may use a straight blade razor while great care is taken to avoid skin cuts. The closeness of the shave can be tested by running a piece of gauze or a cotton ball, wet with 70% isopropyl alcohol, across the shaved scalp. If there is detectable friction or resistance, a closer shave is required.

After shaving, washing the scalp with a mild, fragrance-free shampoo (eg, baby shampoo) will remove some of the sebum of the skin that can interfere with array-to-scalp contact. Dandruff shampoos (which contain pyrithione zinc) also can be used and may offer additional benefit because they have antimicrobial properties. Finally, wiping the skin with 70% isopropyl alcohol will help to remove the naturally occurring scalp sebum, resulting in better contact of the arrays to the scalp. When using alcohol, it is important to avoid contact with areas of dermatitis, erosions, or ulcers, as the alcohol may further irritate the skin.

On subsequent applications of the arrays, use of mineral oil before shaving is recommended because the oil can remove adhesive residues from the prior set of arrays. This will allow for adequate cleansing of the scalp and prevent the accumulation of bacteria and scaly skin.

A



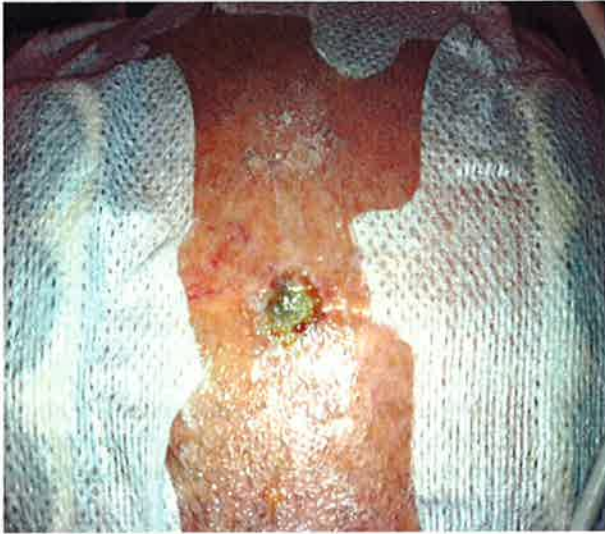
B



**Figure 6.** Skin infection/folliculitis. (A) Folliculitis (62-year-old man after receiving NovoTTF Therapy for 4 weeks). (B) Skin infection (41-year-old woman after receiving NovoTTF Therapy for 3.5 weeks).

**Infection prevention.** The arrays are provided in individual sterile packages to minimize infection risk. Patients and their caregivers are advised to wash their hands prior to application and removal of the transducer arrays. The scalp should be washed with shampoo between array exchanges. The electric





**Figure 7.** Skin ulceration. Note how the arrays are arranged around the site of the ulcer (61-year-old man after receiving NovoTTF Therapy for 2 weeks).

razor should be cleaned (following manufacturer instructions for cleaning) on a regular basis and should not be shared with others.

**Transducer array application.** Arrays are placed on the scalp according to the transducer array layout plan, which is based on head size measurements, tumor size, and tumor location. The ceramic discs of the arrays should not be placed directly over implanted craniotomy closure hardware or surgical scars. Placement of the ceramic disc over a screw or plate may lead to subsequent skin breakdown, erosion, or ulceration.

Every time a set of arrays is changed (approximately every 3–4 days) the position of the arrays should be shifted approximately 0.75 inches from the last location, so that the hydrogel layer is between the prior contact sites. The ceramic discs will leave a slight indentation on the surface of the scalp, allowing patients and caregivers to readily see where to position the new set of arrays. On the next transducer array exchange, arrays should be shifted back to the

**Table 2. Preventive Strategies for Dermatologic Adverse Events**

Category	Guideline for Patient/Caregiver
Shaving and preparation of the scalp	<ul style="list-style-type: none"> <li>• Proper hand washing prior to preparing the scalp for array application</li> <li>• Take time shaving the scalp using gentle but firm circular motions</li> <li>• Ensure a close shave prior to applying the arrays</li> <li>• Cleaning the electric razor <i>after</i> every shave is important to lessen the risk of skin infection</li> <li>• Wash scalp with fragrance-free, mild shampoo (eg, baby shampoo); seborrheic dermatitis shampoo can also be used as it has antibacterial properties (eg, pyrithione zinc 2%, ciclopirox 1%, ketoconazole 2%).</li> <li>• Ensure scalp is completely dry before applying a new set of arrays</li> </ul>
Use of isopropyl (70%) alcohol	<ul style="list-style-type: none"> <li>• Use of first aid antiseptic rubbing alcohol (70% isopropyl alcohol) prior to array application is a necessary step to remove naturally occurring scalp oils, resulting in better adherence of the arrays to the scalp</li> <li>• After shaving and before placing the arrays, wipe the scalp with a gauze or cotton ball soaked in first aid antiseptic rubbing alcohol (70% isopropyl alcohol)</li> <li>• Avoid areas of skin irritation, as the first aid antiseptic rubbing alcohol (70% isopropyl alcohol) may further irritate the skin</li> </ul>
Transducer array exchanges	<ul style="list-style-type: none"> <li>• Change arrays on a regular basis (at least every 3-4 days)</li> <li>• When removing the arrays, avoid “pulling” on the skin and take approximately 60 seconds to remove each array</li> <li>• Using mineral (baby) oil on the edges of the array may make the removal of the adhesive tape easier and less irritating to the skin</li> <li>• To remove leftover array adhesive, use gauze or cotton ball soaked in mineral (baby) oil or pour into hands and gently rub scalp in areas of remaining adhesive</li> <li>• Pay close attention to the scalp at each array exchange and notify the doctor/nurse if there are signs of skin irritation or open areas, in order to receive information on how to treat the affected area(s). Taking a picture of the affected area(s) on the scalp and sharing with doctor/nurse is advised</li> </ul>





**Figure 8.** Preventive measures. Illustration of shifting transducer arrays at each array exchange.

previous position. Shifting the arrays every time they are changed will minimize continuous exposure of the same portion of the scalp to the hydrogel that may lead to subsequent dAEs (Figure 8).

**Transducer array removal.** Each set of arrays should be exchanged at least every 3–4 days. More frequent array exchanges may be required in some patients. Careful removal of arrays (taking approximately 60 seconds to remove each array) will lessen irritation to the skin. When removing the arrays from the scalp, excessive force should be avoided. In addition, applying mineral oil to the edges of the arrays may make removal easier and less irritating to the skin. The use of mineral oil (applied via a soaked gauze or cotton ball or directly to the scalp by hand) will help to ensure complete removal of array adhesive and minimize damage to the skin. Forceful rubbing of the scalp to remove array adhesive should be avoided.

Examination of the scalp at each array exchange by patients and/or caregivers will allow for identification of asymptomatic dAEs and early intervention after consultation with the health care provider. Taking photographs of the affected area(s) on the scalp to review with the physician or nurse in subsequent office visits, or for more urgent consultation and intervention, is recommended.

**Additional considerations.** Because the array hydrogel is hydrophilic, it may become partially liquified (glutinous) during warmer weather or after intense physical activity because the hydrogel will absorb sweat. This may necessitate more frequent changes of the arrays (eg, every 1–2 days). Some medications such as corticosteroids (after prolonged use), systemic chemotherapies, and certain targeted therapies (ie, vascular endothelial growth factor [VEGF] inhibitors such as bevacizumab) may increase the risk of skin reaction or affect wound healing. Ongoing clinical trials evaluating NovoTTF Therapy in combination with other systemic therapies will better define the safety of NovoTTF Therapy with concurrent therapies. A recent presentation of data

from a cohort of 20 patients treated with combined NovoTTF Therapy and bevacizumab did not suggest any concern regarding adverse events in general and dAEs specifically.<sup>47</sup>

### Treatment Interventions—Pharmacologic and Treatment Interruption

The NovoTTF-100A System treatment parameters (frequency and intensity), based on preclinical studies, are preset into the device; therefore, no "dose modifications" can be made for the management of adverse events. Thus, in addition to prophylactic interventions, the primary options for treatment of dAEs are based on the type of dAEs and include topical therapies, relocation of arrays, and avoidance of affected skin whenever possible. Although array shifting to different scalp locations is a recommended prophylactic measure, this can also be used if there are existing sites of dAEs by shifting the arrays around the existing injury sites (Figures 7 and 8). If the area of skin irritation is such that shifting of the arrays is not feasible, the area(s) of skin irritation can be protected with sterile nonadherent dressing pads (Figure 9), while avoiding placement of the ceramic discs directly over these areas. Infrequently, oral antibiotics are required along with treatment interruption for intolerable grade 2 or grade 3 dAEs.

#### Pharmacologic Treatment

The primary treatments for NovoTTF Therapy-related dAEs are topical corticosteroids and topical antibiotics (Figure 10). If there are signs of dermatitis (Table 1), a topical corticosteroid is recommended. However, when the epidermal barrier is compromised (erosions) or when there are signs of infection (Table 3), topical antibiotics are recommended. Obtaining bacterial skin cultures prior to initiating antibiotic therapy is helpful to identify the causative microorganism(s) and to ensure appropriate antimicrobial coverage.

Topical therapies may be applied only at the time of transducer array exchanges (approximately every





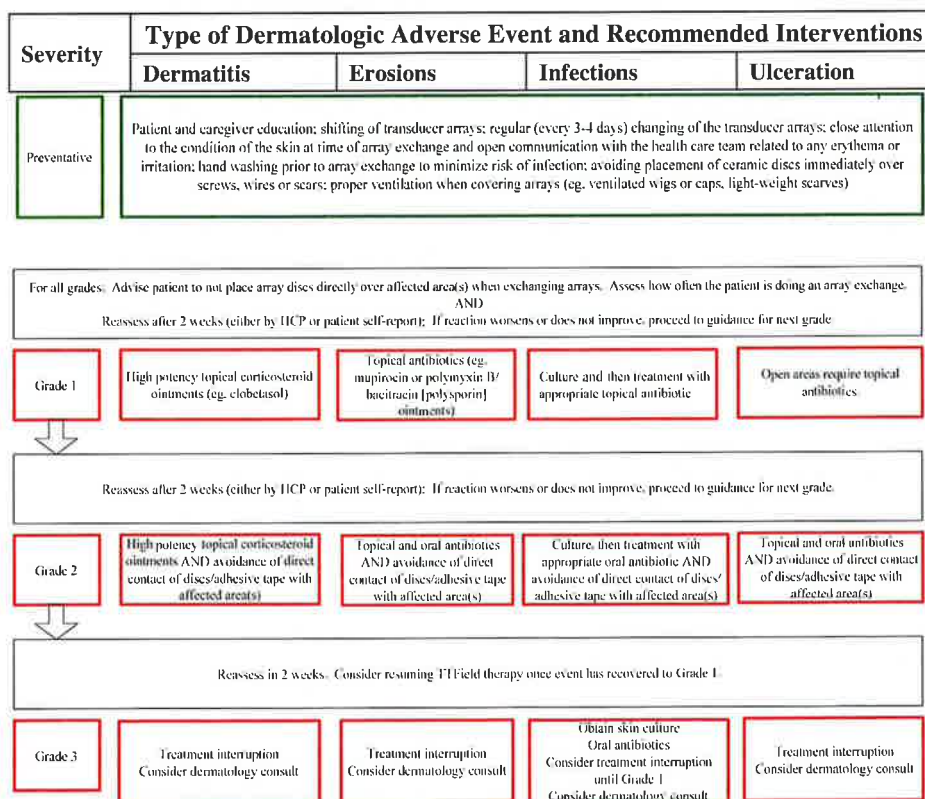
**Figure 9.** Example of protection of sites of dermatologic adverse events with small sterile nonstick gauze barriers. (Note: gauze should not be directly beneath any of the array ceramic disks.)

3–4 days); therefore, high-potency corticosteroid ointments (eg, clobetasol 0.05%, betamethasone 0.05%) are recommended to maximize skin absorption and pharmacological action. Because creams and ointments contain lipid ingredients, it is important that any topical residue left on the skin be removed with scalp washing or 70% isopropyl

alcohol as this residue will interfere with the adherence of the arrays to the scalp and hence may affect transmission of the TTFields. The use of topical or oral antibiotics should be selected based on the spectrum of activity for the skin flora on the scalp (eg, mupirocin or polymyxin B/bacitracin for topical preparations). Use of neomycin-containing topical antibiotics is discouraged because of the relatively high incidence of contact dermatitis in the general population. It is recommended that topical therapies are applied and left on the scalp for a minimum of 15–30 minutes before removing any residual cream/ointment with 70% isopropyl alcohol or re-washing of the scalp and reapplication and relocation of the arrays.

### Treatment Interruptions

For intolerable grade 2 and grade 3 dAEs, treatment interruption in conjunction with topical therapies is recommended. It should be noted that reapplication and relocation of the arrays is possible after treatment interruptions due to intolerable grade 2 or grade 3 events. Anecdotal data suggest that interruption for 2–7 days is frequently sufficient for resolution of the dAEs. This is consistent with the turnover rate of cells in the epidermis as described previously. Patients with prior dAEs may be more likely to have a recurrence of



**Figure 10.** Treatment algorithm for dermatologic adverse events associated with the use of NovoTTF Therapy.



**Table 3. Signs of Skin Events Based on Underlying Pathogenesis**

Dermatitis	Skin Infection	Mechanical	Ischemia
Erythema	Erythema	Erosions	Ulcers
Scaling	Discharge	Abrasions	Pain
Erosions	Pustules	Lacerations	
Edema	Pain	Pain/burning	
Pruritus	Yellow/green crusting		

dAEs once the arrays are reapplied, so patient education and use of prophylactic measures upon rechallenge are recommended.

Duration of treatment interruptions should be minimized, as treatment adherence is correlated with NovoTTF Therapy efficacy. A post hoc, subset analysis from the phase III trial (EF-11) demonstrated a higher OS in patients that were treated for 75% or more of the time (approximately 18 hours per day on average over the course of a month) compared to those patients treated for less than 75% of the time on average (OS 7.8 months *v* 4.5 months, respectively,  $P = .04$ ).<sup>12</sup>

## DISCUSSION AND CONCLUSIONS

NovoTTF Therapy represents a treatment modality for rGB that produces effects on multiple phases of the cell cycle through the use of alternating electric fields (TTFields). It has undergone clinical comparison with systemic chemotherapies in a phase III trial in which NovoTTF Therapy demonstrated a comparable survival benefit, but with improved patient function in cognitive, social, role, and emotional measures, along with decreased systemic adverse events such as anorexia, fatigue, nausea, vomiting.<sup>13</sup> A higher OS was seen in patients that were treated for 75% or more of the time (approximately 18 hours per day on average over the course of a month).<sup>12</sup> Due to its unique mechanism of action and the epicutaneous delivery system with transducer arrays applied on the scalp, dAEs are the most common adverse events seen with this therapy. As with any AE, these dAEs can impact the patients' quality-of-life, adherence to therapy, and medical costs.

A standardized system for clinical description and grading of dAEs related to NovoTTF Therapy is critical in order to ensure proper communication between healthcare providers and to identify appropriate interventions. Characterization of the dAEs observed with NovoTTF Therapy revealed that there are four types of events that differ clinically and that require distinct preventive and active management strategies. These are: (1) irritant contact dermatitis caused by chemical irritation from sweat, hydrogel, and/or alcohol; (2) allergic (immunologic) contact dermatitis resulting from a delayed type

hypersensitivity to tape and/or hydrogel; (3) mechanical erosions from cuts induced by shaving and stripping injury from array removal; (4) ulcers from decreased perfusion where the ceramic discs compress the skin, especially over scars or hardware; and (5) skin infections that are bacterial in origin. Taken as a whole, the pathogenic mechanisms underlying dAEs with NovoTTF Therapy are probably related to the occlusive nature of the adhesive tape of the bandages and hydrogel-covered ceramic discs, rather than to the TTFields generated by the device.

Similar dAEs, including allergic and irritant dermatitis, ulcers, and skin infections, have been described with other devices that are directly applied onto skin, such as abdominal appliances for stomas and ileal conduits.<sup>48,49</sup> To date, there are no randomized controlled trials for the prevention or management of dAEs from the use of abdominal appliances, yet there are abundant anecdotal and empirical data. Indeed, more than 30% of colostomy patients and more than 70% of urostomy and ileostomy patients develop dAEs; however, this unusually high incidence is likely related in part to the enzymatic activity produced by bacteria in the urine and stool. Approximately 30% of visits to stoma nurses are related to skin complications, underscoring the importance of dAEs with epicutaneous devices.<sup>50</sup> Consequently, a similar rationale for the treatment of NovoTTF Therapy-related dAEs has been devised here.

Correct identification of AEs will dictate specific therapies towards their treatment and prevention of recurrence. While most dAEs may be managed with topical interventions and relocation of the arrays, preventive strategies are critical in minimizing recurrent and additional dAEs. For bacterial infections, a swab culture along with topical or oral antibiotics are needed. For erosions or abrasions care should be taken to avoid mechanical trauma and to isolate the lesion from further injury. For ulcers, it is important to remove arrays from the site of the ulcer since they may decrease blood perfusion and interfere with proper wound care. Due to the relatively protracted processes of skin proliferation and wound healing, improvement and resolution of dAEs usually takes at least 7–14 days. Thus, at a minimum, interventions to treat dAEs must continue during this time frame. One notable



**Table 4. Proposed Grading for Device-Related Dermatologic Adverse Events**

Grade	Description*
1	Asymptomatic or mild symptoms; topical therapy indicated (eg, antibiotic, corticosteroid).
2	Moderate symptoms AND topical and systemic therapy indicated (eg, antibiotic, corticosteroid); device application interruption; temporary relocation of device to avoid affected skin areas; or isolation by dressings of affected areas indicated.
3	Severe or medically significant but not immediately life-threatening AND topical and systemic therapy indicated (eg, antibiotic, corticosteroid); operative intervention indicated; hospitalization or prolongation of existing hospitalization indicated; device application interruption indicated.
4	Life-threatening consequences: urgent intervention indicated; device discontinuation indicated.

\* A cutaneous device-related dermatologic event is defined as a disorder characterized by dermatitis, skin infection, erosion, or ulcer related to the noninvasive use of a medical device.

exception is the development of ulcerations. Ulcerations involve the dermis and may require surgical intervention and may demand a longer time to heal even with appropriate wound care.

Treatment interventions will depend on the type and the severity of AE. The severity of AEs is defined by the National Cancer Institute's CTCAE. At the time the phase III NovoTTF Therapy trial was conducted, the CTCAE version 3.0 was used to describe dAEs. Current and previous iterations of the CTCAE (versions 3.0 and 4.0) do not adequately capture the clinical characteristics and management of NovoTTF Therapy-induced dAE.<sup>13</sup> A proposed grading system based on the CTCAE has been described here that includes specific terms related to NovoTTF Therapy-related dAEs (Table 4), including the need for device application interruption or relocation, application of dressings over the affected skin, and indications for topical or systemic therapies. This system may allow for more consistent grading in forthcoming trials investigating the efficacy of NovoTTF Therapy, supportive care interventions and daily clinical care.

Most dAEs can be prevented or managed with the skin care recommendations set forth in this manuscript. With the increasing adoption of NovoTTF Therapy for rGB, proper prevention and timely management of dAEs is crucial to maintain patient quality-of-life, to ensure consistent use of the device, and to maximize the clinical benefit of NovoTTF Therapy for patients with rGB.

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# Clinical Practice Experience With NovoTTF-100A™ System for Glioblastoma: The Patient Registry Dataset (PRiDe)

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Recurrent glioblastoma multiforme (GBM) is a highly aggressive cancer with poor prognosis, and an overall survival of 6 to 7 months with optimal therapies. The NovoTTF-100A™ System is a novel antimitotic cancer therapy recently approved for the treatment of recurrent GBM, based on phase III (EF-11) trial results. The Patient Registry Dataset (PRiDe) is a post-marketing registry of all recurrent GBM patients who received NovoTTF Therapy in a real-world, clinical practice setting in the United States between 2011 and 2013. Data were collected from all adult patients with recurrent GBM who began commercial NovoTTF Therapy in the United States between October 2011 and November 2013. All patients provided written consent before treatment was started. Overall survival (OS) curves were constructed for PRiDe using the Kaplan-Meier method. Median OS in PRiDe was compared for patients stratified by average daily compliance ( $\geq 75\%$  v  $< 75\%$  per day) and other prognostic variables. Adverse events were also evaluated. Data from 457 recurrent GBM patients who received NovoTTF Therapy in 91 US cancer centers were analyzed. More patients in PRiDe than the EF-11 trial received NovoTTF Therapy for first recurrence (33% v 9%) and had received prior bevacizumab therapy (55.1% v 19%). Median OS was significantly longer with NovoTTF Therapy in clinical practice (PRiDe data set) than in the EF-11 trial (9.6 v 6.6 months; HR, 0.66; 95% CI, 0.05 to 0.86,  $P = .0003$ ). One- and 2-year OS rates were more than double for NovoTTF Therapy patients in PRiDe than in the EF-11 trial (1-year: 44% v 20%; 2-year: 30% v 9%). First and second versus third and subsequent recurrences, high Karnofsky performance status (KPS), and no prior bevacizumab use were favorable prognostic factors. No unexpected adverse events were detected in PRiDe.

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As in the EF-11 trial, the most frequent adverse events were mild to moderate skin reactions associated with application of the NovoTTF Therapy transducer arrays. Results from PRiDe, together with those previously reported in the EF-11 trial, indicate that NovoTTF Therapy offers clinical benefit to patients with recurrent GBM. NovoTTF Therapy has high patient tolerability and favorable safety profile in the real-world, clinical practice setting.

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**G**lioblastoma multiforme (GBM) is the most aggressive form of human glioma and accounts for approximately 60% to 70% of all malignant gliomas.<sup>1,2</sup> Based on data from the 2013 Central Brain Tumor Registry of the United States (CBTRUS) statistical report on primary brain and CNS tumors in the United States, an estimated 9,600 to 11,200 new cases of GBM will be diagnosed in 2014.<sup>1,2</sup> Virtually all patients with newly diagnosed GBM relapse despite maximal multimodality treatment,<sup>3</sup> with a median time to recurrence of approximately 7 months.<sup>4</sup> The prognosis for patients with recurrent GBM is even worse. The median progression-free survival (PFS) was only 9 weeks in the pre-bevacizumab era.<sup>5</sup> In 2009, bevacizumab received accelerated approval from the US Food and Drug Administration (FDA) for the treatment for recurrent GBM based on two single-arm studies with favorable response rates and PFS data.<sup>1,6,7</sup> Formal phase III data is not available in the recurrent setting, however phase III comparison of bevacizumab versus placebo in newly diagnosed glioblastoma patients failed to demonstrate prolongation of survival with bevacizumab.<sup>1,8</sup> A major challenge in treatment of recurrent GBM, particularly with bevacizumab, is that the tumor eventually develops resistance to the drug. Moreover, bevacizumab-treated tumors may convert to a more aggressive phenotype and exhibit infiltrative tumor growth as observed on magnetic resonance imaging (MRI).<sup>9,10</sup> Furthermore, patients with recurrent GBM who progress following bevacizumab therapy are typically resistant to subsequent cytotoxic chemotherapies.<sup>1,11,12</sup> Therefore, new treatments that can offer a different mechanism of action and potentially overcome treatment resistance are desperately needed.

The NovoTTF-100A™ System (Novocure, Ltd., Haifa, Israel) is a novel antimitotic cancer therapy approved in 2011 by the US FDA for the treatment of recurrent supratentorial GBM,<sup>13,14</sup> based on the results of a phase III trial comparing NovoTTF Therapy with best chemotherapy according to physician choice.<sup>15</sup> The unique mechanism of action of NovoTTF Therapy involves localized delivery of alternating low-intensity, intermediate-frequency,

tumor-treating fields (TTFields) via non-invasive transducer arrays attached to the patient's scalp.<sup>14</sup> In preclinical studies, TTFields have been shown to selectively kill or arrest the growth of rapidly dividing cancer cells including glioblastoma cell lines by disrupting both mitotic spindle formation and normal cytokinesis by interrupting cytoplasmic furrow formation.<sup>16–20</sup>

The pivotal phase III (EF-11) trial that led to FDA approval of the device compared NovoTTF Therapy (n = 120) with best chemotherapy according to physician's choice (n = 117) in recurrent GBM patients from 28 institutions in seven countries.<sup>15</sup> More than 80% of patients in the study had failed two or more prior chemotherapies, and 20% had experienced recurrence while on bevacizumab. Seventy-eight percent of the 116 patients who started NovoTTF Therapy completed at least one full-treatment course (4 weeks). The results demonstrated comparable median OS with NovoTTF Therapy compared with chemotherapy (6.6 v 6.0 months; hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.66 to 1.12; *P* = .27), together with fewer severe adverse events (6% v 16%, *P* = .022) and improved quality-of-life measures for the NovoTTF Therapy arm compared with the chemotherapy arm. The most common adverse events with NovoTTF Therapy were mild to moderate skin irritation associated with the transducer arrays. Systemic adverse events commonly associated with chemotherapy were generally absent in patients receiving NovoTTF Therapy.

Given the mechanism of action of TTFields and the results of preclinical studies, optimal device compliance is required for therapeutic effectiveness with NovoTTF Therapy. NovoTTF Therapy does not have a half-life, therefore it requires continuous application to exert a therapeutic effect. This differs from systemic chemotherapy, which exerts anticancer effects between administrations due to the drug pharmacokinetics. Based on modeling of tumor growth kinetics and supporting preclinical and clinical data, NovoTTF Therapy must be administered almost "continuously" for at least 4 weeks in order to halt tumor growth and subsequently demonstrate an objective response.<sup>21,22</sup> Recommended administration of NovoTTF Therapy



is  $\geq 18$  hours per day for each 4-week treatment cycle.<sup>21</sup> A post hoc analysis of the phase III trial data recently showed significantly longer median OS in NovoTTF Therapy patients with a maximal monthly compliance rate  $\geq 75\%$  ( $\geq 18$  hours daily) versus those with a  $<75\%$  compliance rate (7.7 *v* 4.5 months,  $P = .042$ ) (see Kanner et al in this supplement). A recent responder analysis also demonstrated very high compliance rates  $>90\%$  in EF-11 responders.<sup>23</sup>

The Patient Registry Dataset (PRiDe) is a registry of 457 recurrent GBM patients who received NovoTTF Therapy in the clinical practice setting on the US commercial prescription-use program between October 2011 and November 2013. Patients treated in clinical trials often differ from those who receive treatment in the real-world setting due to patient selection criteria and frequently represent a less homogenous group. Hence registry data can be an important source of additional information about the efficacy and safety of a newly approved therapy. This report analyzes data from PRiDe to help us better understand the potential benefits of NovoTTF Therapy for patients with recurrent GBM, including analyses of median OS, tolerability, and the relationship between survival and compliance as well as other prognostic factors.

## METHODS

### Patients and Data Collection

PRiDe data were collected from all patients  $\geq 18$  years old with recurrent GBM who began commercial treatment with NovoTTF Therapy in the United States between October 2011 and November 2013. All participating patients provided written informed consent to use protected health information to advance the understanding of NovoTTF Therapy. Recurrent GBM was defined as histologically-confirmed, supratentorial GBM (World Health Organization grade IV astrocytoma) with radiologically confirmed evidence of disease progression, as defined by the Macdonald criteria,<sup>24</sup> following treatment with radiotherapy with or without concomitant and/or adjuvant chemotherapy. Patients who received NovoTTF Therapy were not restricted to the number or types of prior therapies or recurrences. Information about combination use of NovoTTF Therapy as part of the prescription-use program was not captured. Therefore some patients may have received combination therapy (chemotherapy or anti-vascular endothelial growth factor [VEGF] agents) rather than monotherapy.

Baseline characteristics were assessed by manual patient chart review. OS was collected using the Social Security Death Date Registry and obituaries. Novocure started collecting compliance data centrally

in January 2013, so such data are only available for under two thirds of patients in the registry. A monthly compliance assessment was performed for each patient by computer download of an internal log file which captures the cumulative amount of time therapy is delivered to the patient. Patient compliance was calculated as the average percentage of each day the system was delivering fields (out of each 24-hour period). In addition, other prognostic factors, such as the number of prior recurrences, age, KPS, prior bevacizumab use, and any debulking surgery were captured and analyzed. Adverse events were recorded prospectively according to National Cancer Institute Common Toxicity Criteria. Quality-of-life measures were not assessed in PRiDe.

### Statistical Analysis

The OS and treatment duration curves were constructed using the Kaplan-Meier method. OS in PRiDe was compared to OS for patients receiving NovoTTF Therapy or best chemotherapy in the phase III EF-11 trial (ITT population) using a log-rank (Mantel-Cox) test. Patient or disease characteristics prognostic for survival with NovoTTF Therapy were assessed using a Cox proportional hazards model ( $P$  value of .15 for significant interactions). Subgroup analyses were performed on patient/clinical characteristics found to be significantly correlated with OS. A log-rank test was used to compare the relationship between OS and daily compliance ( $<75\%$  *v*  $\geq 75\%$ ), prior debulking surgery (yes, no), KPS (90–100, 70–80, 10–60), recurrence number (1st, 2nd, 3rd–5th recurrence) and prior bevacizumab use (prior use *v* naïve).

## RESULTS

### Patient Characteristics

Four-hundred fifty-seven patients with recurrent GBM were treated with NovoTTF Therapy between October 2011 and November 2013 at 91 oncology centers. This population is more than three times the 120 subjects treated with NovoTTF monotherapy, as well as the 117 subjects treated with chemotherapy, in the phase III EF-11 trial, from which we were making a comparison. Baseline patient characteristics are presented in Table 1. Patient characteristics (age and gender) were generally similar in PRiDe and the two treatment groups in the EF-11 trial. Approximately one third of patients treated commercially with NovoTTF Therapy were women, which is an important observation given the perceived cosmetic considerations of head shaving and array placement.



**Table 1. Baseline Patient Characteristics in PRiDe and EF-11 Trial**

Characteristic		PRiDe NovoTTF Therapy (n = 457)	EF-11 NovoTTF Therapy (n = 120)	EF-11 Chemotherapy (n = 117)
Age (y)	Median (range)	55 (18–86)	54 (24–80)	54 (29–74)
Gender	Male	67.6%	77%	62%
	Female	32.4%	23%	38%
KPS	Median (range)	80 (10–100)	80 (50–100)	80 (50–100)
	10–60	19.0%	NA	NA
	70–80	46.6%	NA	NA
	90–100	30.9%	NA	NA
	Unknown	3.5%	NA	NA
Recurrence	Median (range)	2 (1–5)	2 (1–5)	2 (1–4)
	First	33.3%	9%	15%
	Second	26.9%	48%	46%
	Third to Fifth	27.4%	43%	39%
	Unknown	12.5%	0%	0%
Prior treatments	Bevacizumab	55.1%	19%	18%
	RT + temozolomide	77.9%	86%	82%
	Debulking surgery	63.9%	79%	85%
	Carmustine wafers	3.7%	NA	NA

Abbreviations. KPS, Karnofsky performance status; NA, not available; RT, radiotherapy.

## Tolerability and Safety

No new adverse events were detected in PRiDe compared to those found in EF-11. The most common device-related adverse events associated with NovoTTF Therapy in the registry were skin reactions/irritation and heat sensations on the scalp beneath the transducer arrays (Table 2). Patients sometimes described these events as “warmth” or “tingling” sensations, none of which were associated with injury to the patient. Systemic adverse events, which were often associated with chemotherapy (eg, gastrointestinal, hematologic, and infectious adverse events), were rare for patients treated with NovoTTF Therapy in the registry.

## Survival Rates

Figure 1 presents Kaplan-Meier curves of OS for patients treated with NovoTTF Therapy in the clinical practice setting (PRiDe) and those who received NovoTTF Therapy or best chemotherapy as part of the EF-11 trial (ITT population; see Kanner et al in current supplement). Median OS on NovoTTF Therapy appeared to be markedly longer in PRiDe than in the EF-11 trial (9.6 v 6.6 months). Median OS was also significantly longer with NovoTTF Therapy in PRiDe than with best chemotherapy group in the EF-11 trial (9.6 v 6.0 months). One- and 2-year OS rates for NovoTTF Therapy patients in PRiDe were more than double those seen

with either NovoTTF Therapy or best chemotherapy in the EF-11 trial (Table 3).<sup>15,25</sup>

Median treatment duration for patients in PRiDe was 4.1 months (95% CI, 3.5–4.8). In comparison, the median treatment duration in the EF-11 study was 2.3 months (95% CI, 2.1–2.4) for NovoTTF Therapy arm and 2.1 months (95% CI, 2.0–2.9) for best chemotherapy. Figure 2 shows the fraction of NovoTTF Therapy patients still on treatment over time. Roughly 50% were still on NovoTTF Therapy after 4 months from treatment start, and roughly 10% were still on NovoTTF Therapy at 2 years after treatment start.

## Compliance as a Prognostic Factor and Its Relationship to OS

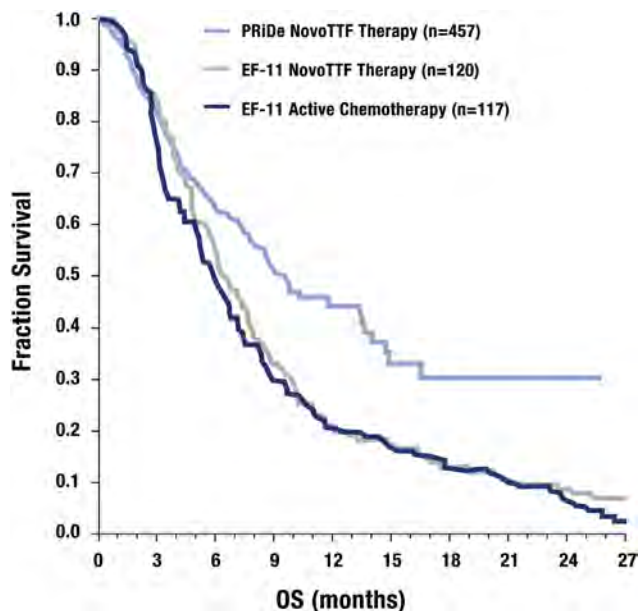
Because of the major difference in the OS in patients registered in PRiDe as compared to the OS of subjects treated with NovoTTF monotherapy in EF-11, we sought to identify the prognostic factors in the former cohort. The first prognostic factor we analyzed was NovoTTF treatment compliance because it was found to be prognostically important in EF-11 in a post hoc analysis. Compliance data were collected centrally starting in January 2013 and, therefore, were only available for 287 of the 457 patients (63%) in the registry. The median daily compliance was 70% for patients treated with NovoTTF Therapy in PRiDe (range, 12%–99%). One



**Table 2.** Adverse Events in Patients With Recurrent Glioblastoma Multiforme Treated With NovoTTF Therapy in PRiDe

Adverse event	Percentage of Patients PRiDe (n = 457)
Skin reaction	24.3
Heat sensation	11.3
Neurological disorder	10.4
Seizure	8.9
Electric sensation	7.7
Headache	5.7
Pain/discomfort	4.7
Fall	3.9
Psychiatric disorder	2.9
Gastrointestinal disorder	2.9
Fatigue	2.5
Vascular disorder	1.6
Weakness	1.4
Infections	1.4
Eye disorder	1.3

hundred twenty-seven (44%) achieved daily compliance of  $\geq 75\%$  of each day, while 160 (56%) had daily compliance of  $< 75\%$ . As illustrated in Figure 3, median OS was significantly longer in patients with a NovoTTF Therapy daily compliance  $\geq 75\%$  than in those with  $< 75\%$  daily compliance (13.5% *v* 4.0%; HR, 0.43; 95% CI, 0.29–0.63;  $P < .0001$ ).

**Figure 1.** Kaplan-Meier overall survival (OS) curves for patients with recurrent glioblastoma multiforme treated with NovoTTF Therapy in PRiDe or with NovoTTF Therapy or best chemotherapy in the EF-11 trial ( $P = .0003$ ).

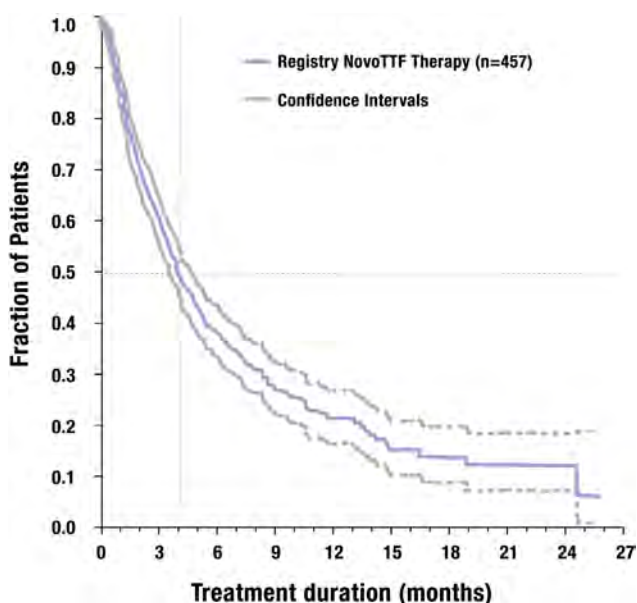
## Other Prognostic Factors

The Cox proportional hazards model identified the presence or absence of debulking surgery, number of prior recurrences, compliance, KPS, and prior bevacizumab therapy as significant independent predictors of OS in patients treated with NovoTTF Therapy in PRiDe ( $P < .15$ ). Table 4 presents log-rank OS testing between patient subgroups in PRiDe for each of these prognostic factors; Figure 4 presents Kaplan-Meier survival curves for these same factors. First, no difference in median OS was observed between patients who did not have surgical debulking and those who did (8.9 *v* 9.8, respectively; HR, 1.1; 95% CI, 0.8–1.5;  $P = .7927$ ). Second, recurrent GBM patients treated with NovoTTF Therapy in clinical practice at their first recurrence experienced a significantly longer median OS as compared to patients treated at their second, third, or subsequent recurrence (20 months compared to 8.5 and 4.9 months, respectively; HR, 0.6; 95% CI, 0.4–0.9;  $P = 0.0271$  and HR, 0.3; 95% CI, 0.2–0.5;  $P < .0001$ ). It should be noted that a greater percentage of patients in PRiDe were at their first GBM recurrence compared with patients treated with NovoTTF Therapy or best chemotherapy in the EF-11 trial (33.3% *v* 9% and 15%, respectively). In addition, differences were also apparent between patients in PRiDe and those in the EF-11 trial with respect to prior treatments. More than half of NovoTTF Therapy patients in PRiDe had previously received bevacizumab (55.1%), compared with only 19% of NovoTTF monotherapy and 18% of best active chemotherapy cohorts in the EF-11 trial. Third, recurrent GBM patients with KPS  $\geq 90$  exhibited a near doubling of median OS compared with patients with a KPS of 70–80, median OS 14.8 versus 7.7 months, respectively, HR 0.6 (95% CI, 0.4–0.9),  $P = .0070$ . Lastly, the survival of bevacizumab-naïve patients was significantly longer compared to patients who had received prior bevacizumab before starting NovoTTF Therapy, with a respective median OS 13.4 versus 7.2 months, HR 0.5 (95% CI, 0.4–0.7),  $P < .0001$ . These data suggest that, within this

**Table 3.** One- and 2-Year Overall Survival Rates for Patients With Recurrent Glioblastoma Multiforme Treated With NovoTTF Therapy in PRiDe and EF-11 Trial, and With Best Chemotherapy in the EF-11 Trial

Endpoint	PRiDe NovoTTF Therapy (n = 457)	EF-11 NovoTTF Therapy (n = 120)	EF-11 Chemo- therapy (n = 117)
1-Year survival	44%	20%	20%
2-Year survival	30%	9%	7%





**Figure 2.** Fraction of NovoTTF Therapy patients alive by treatment duration (PRiDe).

heterogeneous group of patients registered in PRiDe, there were subsets of patients who derived significant benefit from NovoTTF Therapy.

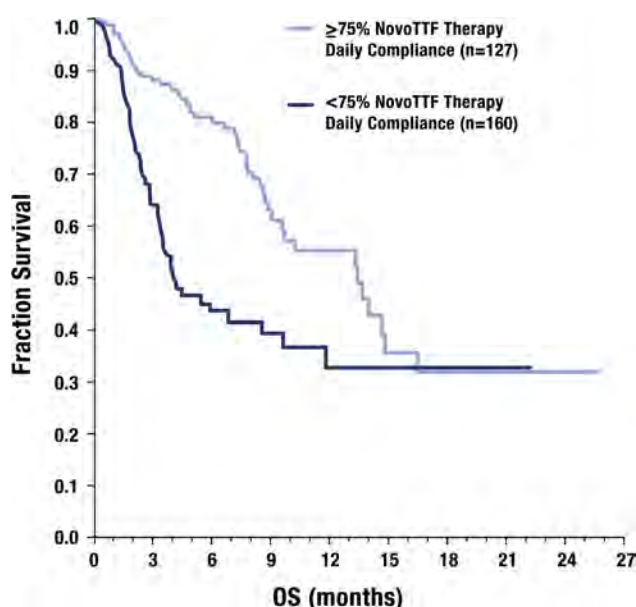
## DISCUSSION

The Patient Registry Dataset, or PRiDe, represents 457 unselected patients with recurrent GBM who received NovoTTF Therapy in a real-world, clinical practice setting across 91 cancer centers in the United States between October 2011 and November 2013. No new, unexpected adverse events were detected with NovoTTF Therapy in this cohort. Similar to the EF-11 trial,<sup>15</sup> the most common adverse events associated with NovoTTF Therapy were mild to moderate skin reactions localized to the scalp beneath the transducer arrays. These reactions were easily treated with topical corticosteroids or antibiotics, were not associated with serious injury to the scalp, and typically did not require interruption of treatment. Some patients in PRiDe reported subjective sensations beneath the transducer arrays, often described as “warmth” or “tingling.” These heat or electric sensations were captured as adverse events in PRiDe (“skin reaction”), but not in the EF-11 trial. These sensations occur when the contact between transducer arrays and the skin is suboptimal, and usually indicate the presence of hair regrowth. In these instances, re-shaving the head can re-establish optimal contact between the skin and transducer arrays. Furthermore, systemic adverse events commonly observed with chemotherapy were largely absent in patients treated with

NovoTTF Therapy in PRiDe as they were in the EF-11 trial.<sup>15</sup>

Patients receiving NovoTTF Therapy for recurrent GBM demonstrated a median OS of 9.6 months in clinical practice. This compares favorably to the reported median OS for the EF-11 pivotal trial cohort treated with NovoTTF monotherapy, where median OS was 6.6 months, and to OS of patients who received treatments for recurrent GBM in other clinical trials.<sup>26–29</sup> For example, recent reports of median OS in recurrent GBM patients treated with bevacizumab are in the range of 6 to 10.5 months,<sup>7,12,26–28,30</sup> and those treated with temozolomide in the range 6 to 9 months.<sup>31–33</sup> It should be noted that many of the longer term survival outcomes noted in clinical trials of bevacizumab and temozolomide in recurrent GBM included small sample sizes and none were randomized.

The difference between the OS seen in clinical practice and in the EF-11 trial may in part be due the greater percentage of patients with a first GBM recurrence in PRiDe versus patients in the EF-11 study (33.3% *v* 9%, respectively). This observation is also supported by a prior post hoc analysis of EF-11 that showed a significantly longer median OS in patients treated with NovoTTF Therapy at their first or second recurrence compared to those treated at third or subsequent recurrences. Furthermore, when used as intended (daily compliance  $\geq 75\%$  or  $\geq 18$  hours daily), the median OS for patients treated with NovoTTF Therapy in PRiDe was remarkably high at 13.5 months compared to only 4.0 months in those who had suboptimal compliance (daily compliance



**Figure 3.** Overall survival (OS) by daily compliance with NovoTTF Therapy for recurrent glioblastoma multiforme patients in PRiDe.



**Table 4.** Overall Survival (OS) in Patients With Recurrent Glioblastoma Multiforme Treated With NovoTTF Therapy in PRiDe Based on Prognostic Factors Significantly Correlated With OS in the Cox Proportional Hazards

Variable	Median OS (mo)	Hazard Ratio	P Value
<b>No. of recurrences</b>			
1st	20	—	—
2nd	8.5	0.6 (95% CI, 0.4–0.9)	.0271 <sup>a</sup>
3rd–5th	4.9	0.3 (95% CI, 0.2–0.5)	<.0001 <sup>b</sup>
<b>Compliance</b>			
≥75%	13.5	0.4 (95% CI, 0.3–0.6)	<.0001
<75%	4.0		
<b>Karnofsky performance status (KPS)</b>			
90–100	14.8	—	—
70–90	7.7	0.6 (95% CI, 0.4–0.9)	.0070 <sup>c</sup>
10–60	6.1	0.4 (95% CI, 0.2–0.6)	<.0001 <sup>d</sup>
<b>Bevacizumab use</b>			
Naïve	13.4	0.5 (95% CI, 0.4–0.7)	<.0001
Prior use	7.2		
<b>Debulking surgery</b>			
No	8.9	1.1 (95% CI, 0.8–1.5)	.7927
Yes (any surgery)	9.8		

<sup>a</sup> First recurrence compared to 2nd recurrence.<sup>b</sup> First recurrence compared to 3rd–5th recurrence.<sup>c</sup> KPS 90–100 compared to KPS 70–80.<sup>d</sup> KPS 90–100 compared to KPS 10–60.

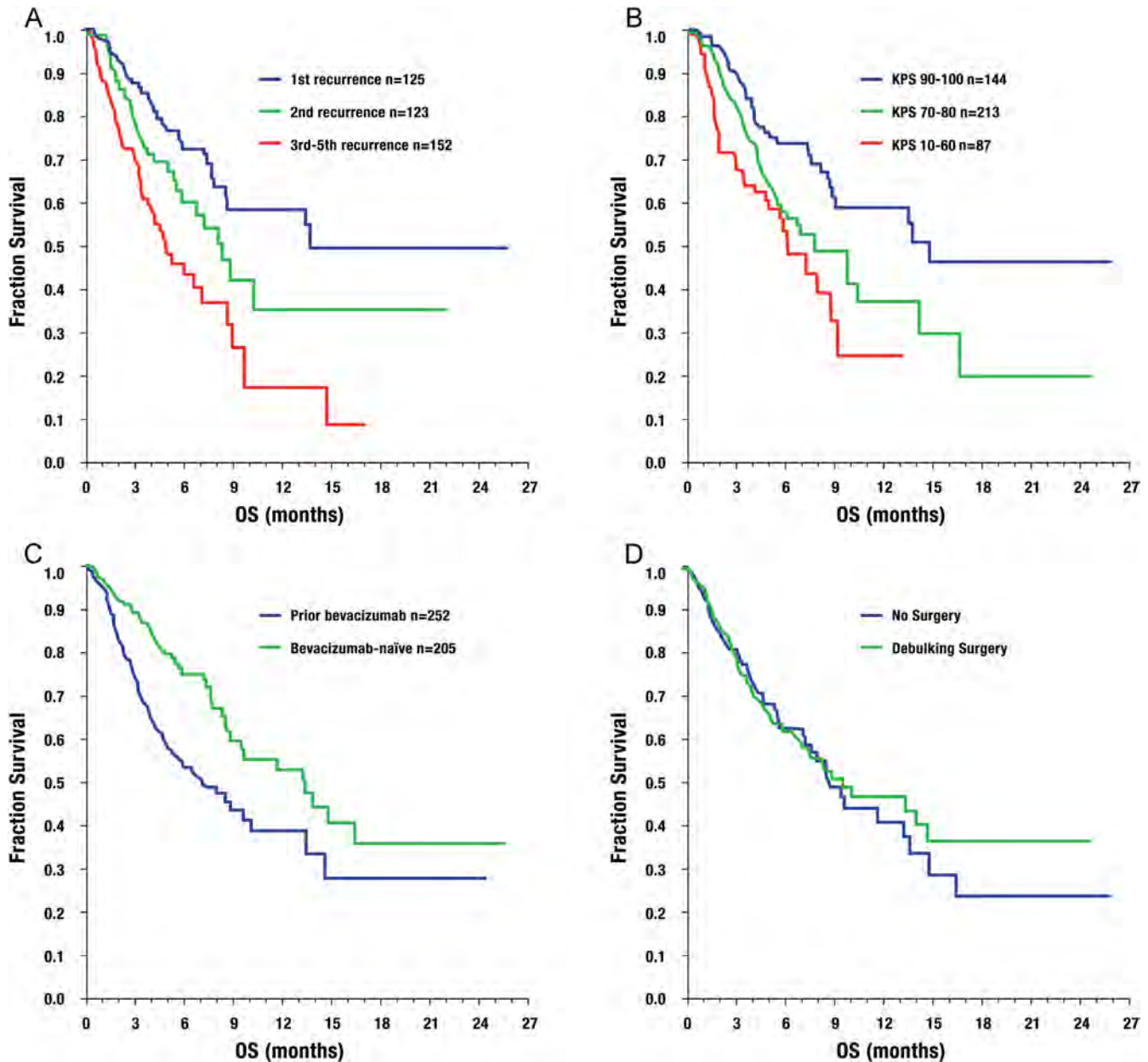
<75% or <18 hours daily). Kanner et al (see accompanying Kanner article in this supplement) recently reported similar findings when re-examining data from the EF-11 trial: median OS was significantly longer with a monthly compliance rate for NovoTTF Therapy ≥75% than <75% (7.7 v 4.5 months,  $P = .042$ ). The compliance findings from each of these studies are consistent with the mechanism of action of NovoTTF Therapy, which depends on almost continuous administration (≥18 hours per day) for a prolonged period of time (≥4 weeks).<sup>21,22</sup> However, patients in PRiDe who had suboptimal compliance were also found to have lower KPS and were, in general, at later stages of their disease. It is unclear whether they also may have had larger tumors or inadequate social support. Nevertheless, consistent with previous findings, our data suggest that applying NovoTTF Therapy to patients with higher performance status, earlier in their recurrence and ensuring treatment compliance, can maximize clinical benefit.

Additional analyses uncovered other prognostic factors that were important for patients in PRiDe. Of interest, in our subgroup analysis, 55.1% of patients in PRiDe who received prior bevacizumab therapy demonstrated a shorter median OS of 7.2 months, as compared to a median OS of 13.4 months in bevacizumab-naïve patients. The shorter survival in patients treated previously with bevacizumab may be a result of acquired tumor resistance and development of a more aggressive phenotype with

infiltrative tumor progression on MRI.<sup>9,10</sup> Moreover, patients with recurrent GBM tumors that progress while on bevacizumab therapy are typically resistant or refractory to subsequent cytotoxic chemotherapy,<sup>1,11,12</sup> and have a median OS of just 2.7 months. Therefore, the PRiDe data suggest that at least a percentage of bevacizumab-resistant tumors remain responsive to NovoTTF Therapy. Future analysis of responders and nonresponders to NovoTTF Therapy will need to include molecular genetic analysis of the tumor (and especially MGMT methylation status), the estimated tumor size (volume) as measured by fluid attenuated inversion recovery sequence on MRI, and more detailed analysis of the extent of resection.

Our analysis of KPS in PRiDe also demonstrated that higher KPS correlated with longer OS. It is unclear at this time whether or not patients who had KPS 90–100 had smaller tumors than the rest of the cohort or perhaps more extensive resections. KPS is often, but not always, a measure of tumor size, particularly the microscopic invasive component of the glioblastoma. Whether or not the median tumor size, as measured by gadolinium-enhanced T1-weighted and/or FLAIR MRI, differ between the subgroup with KPS 90–100 versus 70–90 and 10–60 remains to be determined. Of note, age was not a predictor of OS in the PRiDe dataset when evaluated either by direct correlation (Pearson correlation coefficient) or a





**Figure 4.** Kaplan-Meier overall survival (OS) curves for recurrent glioblastoma multiforme patients treated with NovoTTF Therapy in PRiDe based on (A) recurrence number, (B) Karnofsky performance status (KPS), (C) prior bevacizumab use, and (D) prior debulking surgery, respectively.

Cox proportional hazards model ( $P = .20$ ). In addition, age was not correlated with compliance in the PRiDe (correlation coefficient = 0.02;  $P = .37$ ). Taken in the context of the overall efficacy results, these findings suggest NovoTTF Therapy works well for patients of all ages and that advanced age is not associated with lower compliance. It would also be interesting to know if marital status (or other measures of patient support) influence compliance and survival, but data on marital status were not collected in PRiDe.

Finally, the PRiDe dataset did not capture patients on combination treatments in which additional

biologic therapy or chemotherapy were added to NovoTTF Therapy. It is possible that the longer survival seen in clinical practice with NovoTTF Therapy compared to NovoTTF monotherapy in the EF-11 trial is a reflection of combination use of NovoTTF Therapy with biological agents or cytotoxic chemotherapy. In fact, preclinical data have suggested that TTFields are additive or even synergistic with chemotherapies in cell culture.<sup>34-36</sup> Therefore, the potential benefits of combining NovoTTF Therapy with other systemic therapies warrant further investigation. A phase III trial of NovoTTF Therapy together with temozolomide



compared to temozolomide alone is currently ongoing in patients with newly diagnosed glioblastoma. The results of this trial will shed light on the possible additive or synergistic effects of NovoTTF Therapy and systemic chemotherapy.

In summary, PRiDe and the EF-11 trial represent one of the largest datasets of patients with recurrent GBM published to date, containing 700 patients in total, 567 of whom were treated with NovoTTF Therapy. The results, individually and collectively, provide further support for the use of NovoTTF Therapy to treat recurrent, supratentorial GBM. Observations from the post-marketing registry demonstrate that the safety and efficacy observed with NovoTTF Therapy in a clinical trial extend to the real-world, clinical practice setting. Future investigations may need to include NovoTTF Therapy in combination with other recurrent GBM treatments, which together may have additive or synergistic effects on patient outcomes.

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## Long-term survival of patients suffering from glioblastoma multiforme treated with tumor-treating fields

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The NovoTTF-100A System is approved for the treatment of patients with recurrent GBM.  
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CASE REPORT

Open Access

# Long-term survival of patients suffering from glioblastoma multiforme treated with tumor-treating fields

Aaron Michael Rulseh<sup>1</sup>, Jiří Keller<sup>1,2</sup>, Jan Klener<sup>3</sup>, Jan Šroubek<sup>3</sup>, Vladimír Dbalý<sup>3</sup>, Martin Syřůček<sup>4</sup>, František Tovaryš<sup>3</sup> and Josef Vymazal<sup>1,5\*</sup>

## Abstract

Glioblastoma multiforme (GBM) is the most common and malignant primary intracranial tumor, and has a median survival of only 10 to 14 months with only 3 to 5% of patients surviving more than three years. Recurrence (RGBM) is nearly universal, and further decreases the median survival to only five to seven months with optimal therapy. Tumor-treating fields (TTField) therapy is a novel treatment technique that has recently received CE and FDA approval for the treatment of RGBM, and is based on the principle that low intensity, intermediate frequency electric fields (100 to 300 kHz) may induce apoptosis in specific cell types. Our center was the first to apply TTField treatment to histologically proven GBM in a small pilot study of 20 individuals in 2004 and 2005, and four of those original 20 patients are still alive today. We report two cases of GBM and two cases of RGBM treated by TTField therapy, all in good health and no longer receiving any treatment more than seven years after initiating TTField therapy, with no clinical or radiological evidence of recurrence.

**Keywords:** Glioblastoma multiforme, Recurrent glioblastoma multiforme, Tumor-treating fields, Long-term survival

## Background

Glioblastoma multiforme (GBM) is the most common and malignant primary intracranial tumor, representing as much as 30% of primary brain tumors with increasing incidence in some geographic regions [1]. Its incidence has been shown to increase with age [2]. Despite the introduction of aggressive treatment with temozolomide, the median survival time of adult patients remains approximately 10 months and as high as 14 months in patients receiving combined treatment with radiotherapy [3]. Only 3 to 5% of patients survive more than three years [4], and sporadic reports of survival exceeding five years are rare [5]. The exact clinical and molecular factors that contribute to such long-term survival are still unknown; however, younger age and a high Karnofsky performance scale (KPS) are considered prognostically favorable factors [4]. Recently, MGMT gene promoter

methylation and IDH1 mutation have been shown to correlate with longer survival as well [6]. Recurrence of GBM is nearly universal, and patients with recurrent glioblastoma multiforme (RGBM) fare even worse, with a median survival of only five to seven months with optimal therapy [7].

Tumor-treating fields (TTField) therapy is a novel treatment technique with the potential to treat various forms of cancer. TTField therapy is based on the principle that low intensity, intermediate frequency electric fields (100 to 300 kHz) have an anti-mitotic effect which acts during late metaphase and anaphase, with specific frequencies affecting specific cell types [8]. The applied fields disrupt mitotic spindle microtubule assembly and the segregation of intracellular organelles during cell division, leading to apoptosis [9]. TTField therapy has been tested in patients with advanced non-small cell lung cancer [10] and has recently received CE and FDA approval for the treatment of RGBM based on the results of a phase III clinical trial [11].

Our center was the first in the world to apply TTField treatment to histologically proven GBM patients in a

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**Table 1 Participant baseline characteristics**

Patient no.	Group	Date of birth	Date of inclusion	Age at inclusion	Gender	Weight (kg)	KPS (%)	Tumor location
1	RGBM	07/1950	05/2004	53.8	Male	70	100	R. Temporoparietal
2	RGBM	08/1945	05/2004	58.8	Male	83	100	R. Temporal
<b>3*</b>	<b>RGBM</b>	<b>06/1952</b>	<b>08/2004</b>	<b>52.2</b>	<b>Female</b>	<b>65</b>	<b>70</b>	<b>R. Parietal</b>
<b>4*</b>	<b>RGBM</b>	<b>08/1961</b>	<b>08/2004</b>	<b>43.1</b>	<b>Male</b>	<b>85</b>	<b>100</b>	<b>L. Frontoparietal</b>
5	RGBM	05/1937	10/2004	67.5	Male	83	80	R. Temporoparietal
6	RGBM	05/1953	01/2005	51.7	Male	103	70	R. Parietooccipital
7	RGBM	04/1950	01/2005	54.8	Male	85	90	R. Frontotemporal
8	RGBM	06/1966	06/2005	39	Male	72	100	R. Temporoparietal
9	RGBM	06/1977	08/2005	28	Female	70	90	L. Temporoparietooccipital
10	RGBM	08/1948	09/2005	57	Female	68	70	L. Temporal
11	GBM	11/1968	01/2005	36	Male	77	100	L. Frontal
12	GBM	04/1935	05/2005	70	Male	79	90	R. Temporal
<b>13*</b>	<b>GBM</b>	<b>12/1973</b>	<b>10/2005</b>	<b>32</b>	<b>Male</b>	<b>85</b>	<b>100</b>	<b>R. Frontal</b>
14	GBM	03/1948	01/2006	58	Male	81	100	R. Temporal
15	GBM	10/1963	01/2006	42	Male	96	90	R. Temporal
16	GBM	03/1961	01/2006	45	Female	50	100	R. Frontal
<b>17*</b>	<b>GBM</b>	<b>08/1973</b>	<b>04/2006</b>	<b>33</b>	<b>Female</b>	<b>65</b>	<b>90</b>	<b>R. Frontal</b>
18	GBM	07/1951	10/2006	55	Male	80	100	L. Occipital
19	GBM	05/1941	09/2006	65	Male	85	80	L. Frontotemporal
20	GBM	05/1951	01/2007	56	Male	82	90	R. Temporal

\* case in present report.

small pilot study of 20 individuals in 2004 and 2005 (Table 1). The inclusion criteria of the study included a KPS  $\geq 70\%$  and age  $\geq 18$  years, and the patients were divided into two groups. The first group consisted of 10 patients diagnosed with RGBM after failing temozolomide treatment that were treated with TTField therapy alone [9]. The second group consisted of 10 newly diagnosed GBM patients at least four weeks post radiation therapy (with adjuvant temozolomide) [12] that received TTField therapy combined with maintenance temozolomide. The treatment duration in individual patients varied between one and one and a half years, and all histological samples were independently examined in two laboratories in two countries. We report two cases of GBM and two cases of RGBM treated by TTField therapy, all in good health and no longer receiving any treatment more than seven years after initiating TTField treatment, with no clinical or radiological evidence of recurrence.

Baseline characteristics of all 20 participants in the original pilot study. Dates are presented as month/year for simplicity, age calculations were performed on exact dates.

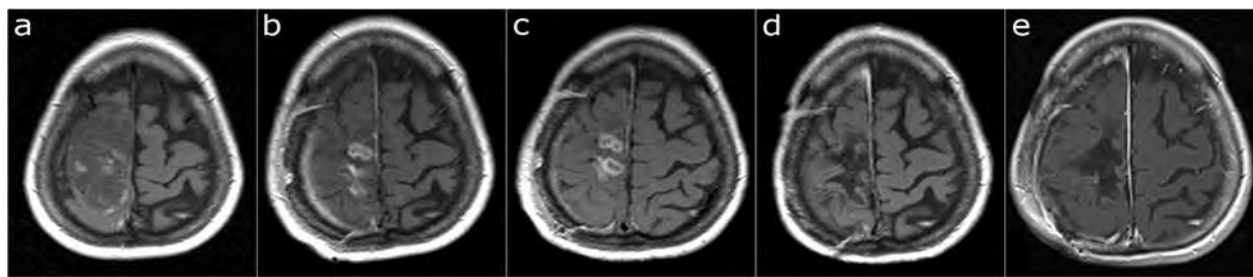
GBM, glioblastoma multiforme (newly diagnosed); KPS, Karnofsky performance scale; L., left; No., number; R., right; RGBM, recurrent glioblastoma multiforme.

## Case presentation

### Case 1

A 52-year-old woman with a history of epileptic seizures and left-sided hemiparesis was diagnosed with an intra-axial brain tumor, suspected to be a high-grade glioma based on the magnetic resonance imaging (MRI) findings (Figure 1a). The tumor was resected with the help of functional blood oxygen level dependence (BOLD-fMRI) neuronavigation in April 2004. Gross total resection was performed and pathological analysis revealed clear evidence of glioblastoma. Standard radiotherapy (60 Gy) and chemotherapy with temozolomide followed. After radiotherapy and chemotherapy, a follow-up MRI in July 2004 showed two enhancing lesions that were highly suspected to be tumor recurrence (Figure 1b). TTField therapy was initiated in August 2004 as monotherapy. In September 2004, one month after starting TTField therapy, one of the enhancing lesions increased in size (Figure 1c); however, treatment with TTField therapy was continued since the progression was asymptomatic. By February 2005, both enhancing lesions had disappeared (Figure 1d) and are no longer detectable (Figure 1e). TTField treatment was discontinued after one year in August 2005, with no treatment administered after that time. The last MR examination from August 2011 shows no evidence of enhancing tumor.





**Figure 1 Serial MR imaging in Case 1.** T1-weighted image after application of contrast agent. **a)** April 2004, before surgery. GBM located in the right central region. **b)** July 2004, post-operative radiotherapy and chemotherapy. Two enhancing lesions present. **c)** September 2004, one month after the start of TTField therapy. The dorsal enhancing lesion increased in size, highly suspicious of tumor recurrence. **d)** June 2005, TTField treatment. No enhancing lesion present. **e)** August 2011. No enhancing lesion present. GBM, glioblastoma multiforme; MR, magnetic resonance; TTField, tumor-treating fields.

The patient has mild, residual left-sided hemiparesis, and otherwise feels completely healthy with no subjective complaints and a KPS of 90.

#### Case 2

A 41-year-old male presented with pronunciation difficulties in December 2003. Neurological examination revealed slight right-sided hemiparesis, and MRI revealed an intra-axial tumor suspected to be high-grade glioma (Figure 2a). Surgery was delayed due to intercurrent infection (influenza) until March 2004, and the tumor was then partially resected. Pathological analysis revealed histological characteristics of glioblastoma. Standard radiotherapy (60 Gy) and chemotherapy with temozolomide followed. A follow-up examination in August 2004 showed an enhancing lesion suspected to be a recurrent tumor (Figure 2b). TTField therapy was initiated in August 2004. By March 2005 the enhancing tumor had progressed and become cystic (Figure 2c). Again, treatment with TTField therapy was continued due to the asymptomatic nature of this progression. By October 2005 the tumor had regressed (Figure 2d) while the patient was still receiving TTField therapy. TTField therapy was discontinued in February 2006. A discrete, enhancing lesion is still present (last MRI in November 2011, Figure 2e). This small, enhancing lesion was examined with MR spectroscopy (Figure 2f) and showed noise-signal only, while the spectra in neighboring voxels were practically normal (Figure 2g). Positron emission tomography (PET) did not reveal any tumor-like patterns. The patient is in good health, has minor difficulties with speech, and is completely independent, with a KPS of 90 to 100.

#### Case 3

A 31-year-old male presented with an epileptic seizure in January 2005. MRI examination revealed a tumor in the right frontal lobe that was suspected to be a high grade glioma (Figure 3a). The tumor was totally resected

macroscopically (gross total resection) and showed clear histopathological characteristics of glioblastoma (World Health Organization (WHO) grade IV). Standard radiotherapy (60 Gy) and chemotherapy with temozolomide followed. TTField treatment was started in October 2005 concomitant to maintenance temozolomide and both treatments were discontinued in October 2006. Since that time, no tumor recurrence has been detected (Figure 3b). The patient is in good health, off all treatment and with a KPS of 100.

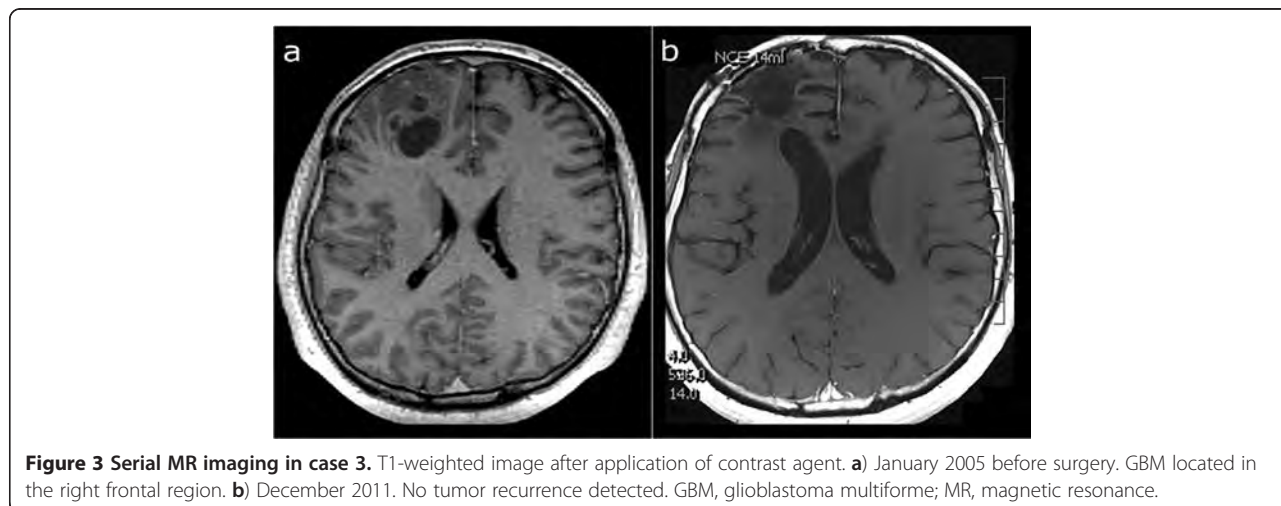
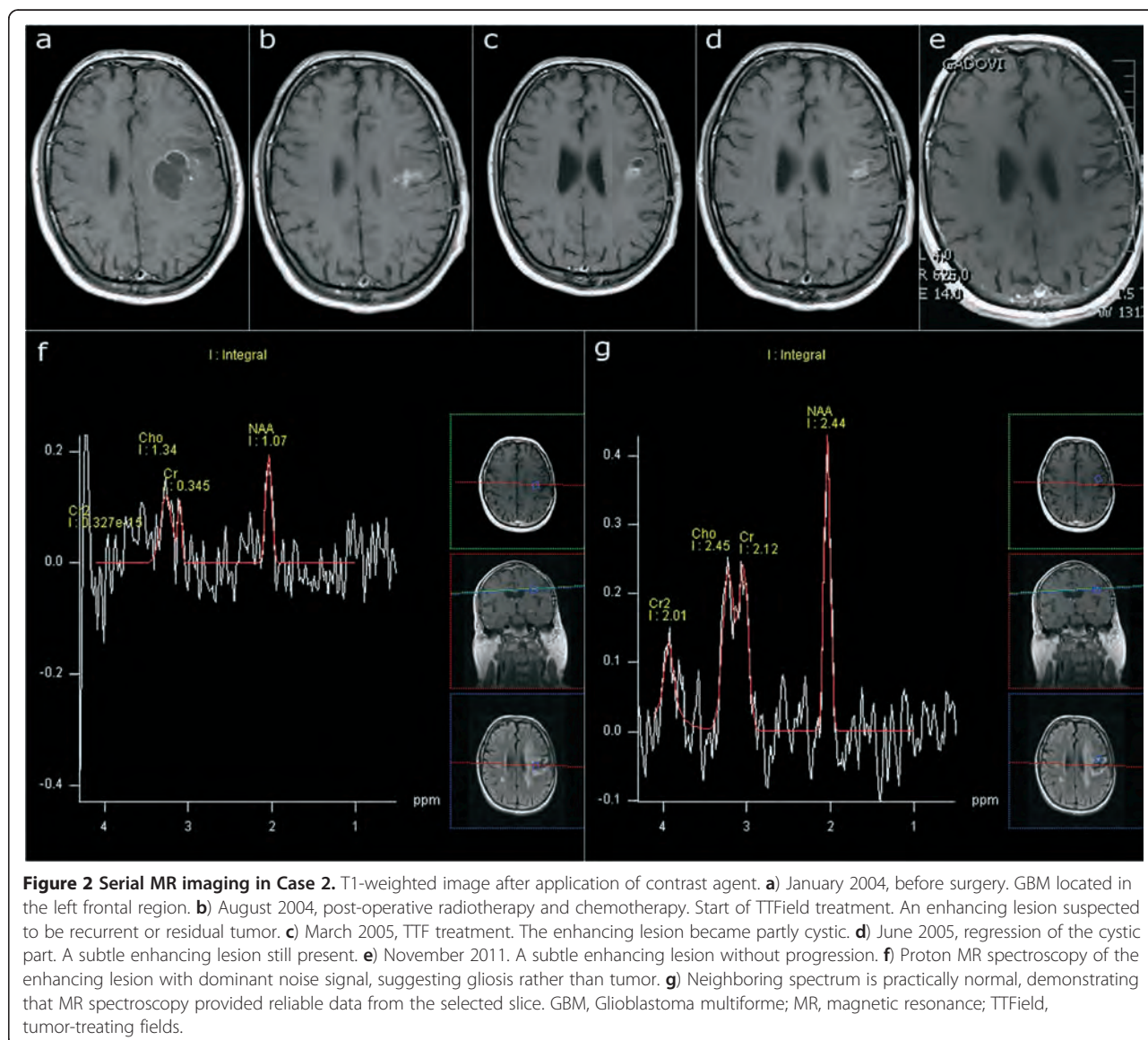
#### Case 4

A 33-year-old female underwent MRI of the brain following an epileptic seizure in November 2005. A tentative diagnosis of high-grade glioma was made based on MRI findings (Figure 4a). The tumor was completely resected macroscopically (gross total resection) in February 2006 and showed clear histopathological characteristics of glioblastoma (WHO grade IV). Standard radiotherapy (60 Gy) and chemotherapy with temozolomide followed. No recurrence was noted on follow-up MRI in February 2007 (Figure 4b). TTField treatment was started in April 2006 concomitant to maintenance temozolomide and both treatments were discontinued in April 2007. No tumor recurrence has been detected on a number of follow-up MRI examinations (Figure 4c), the last of which was performed in September 2011. MR spectroscopy in a small volume of tissue with corresponding increased signal intensity on Fluid Attenuated Inversion Recovery (FLAIR) images did not show a tumor-like pattern (Figure 4d). Currently the patient is off all treatment, in good health, with a KPS of 100.

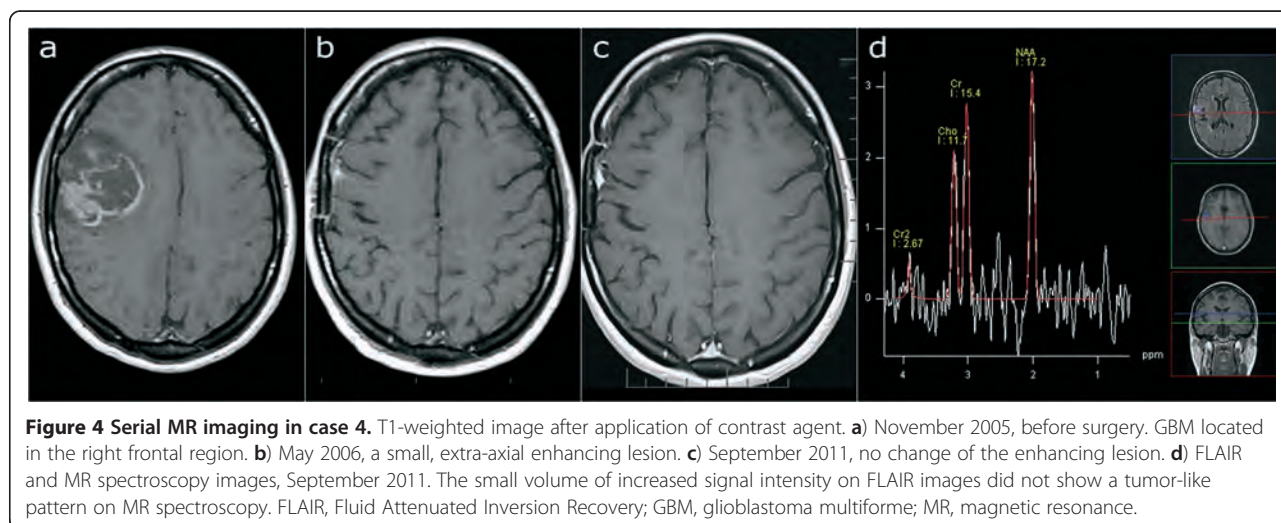
#### Discussion

Despite multi-modal treatment, the prognosis of GBM remains poor. Recurrence is likely inevitable provided the patient survives long enough, and further reduces the median survival to only five to seven months [4,7]. There have been documented cases of GBM patients









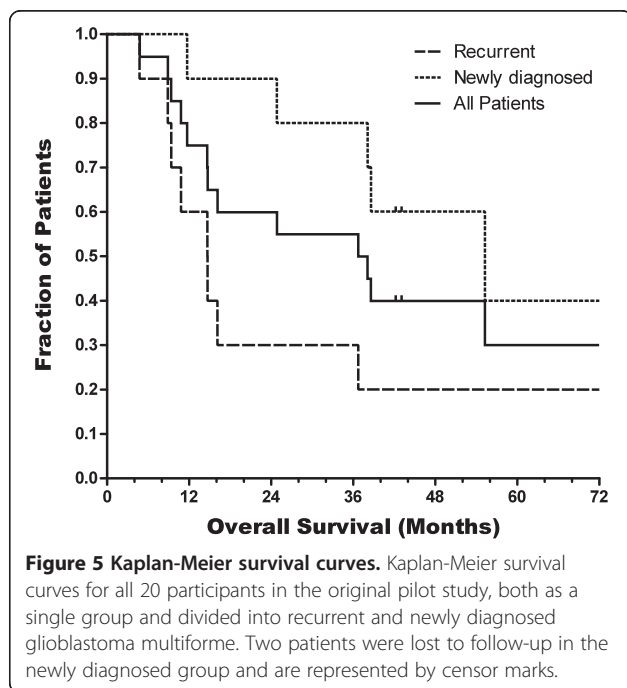
surviving longer than three years, termed long-term survival (LTS), representing approximately three to five percent of GBM patients [4]. Survival of GBM patients longer than five years, however, is exceptional, representing as few as 0.5% of patients [5].

Twenty percent of the participants in our pilot study (4 out of 20) have survived until the time of this report, roughly seven years (Figure 5). These individuals continue to undergo regular neurological and radiological examinations, and do not show any signs of recurrence. The data from standard MR imaging are further supported by MR spectroscopy that does not show any

tumor-like patterns in regions with corresponding abnormal signal intensity.

Younger age and a higher KPS have been proposed as prognostically favorable parameters for longer survival [4]. The mean age of our LTS-RGBM patients (Cases 1 and 2) was 47.5 years compared to 51.5 years for the rest of the RGBM group [9]. This difference is not striking. Although we cannot completely exclude pseudo-progression or radiation necrosis in these patients diagnosed without histological verification of the recurrent lesion, their continued survival is still remarkable. In the group of newly diagnosed GBM, the mean age of LTS-GBM patients (Cases 3 and 4) was 32 years compared to 51 years for the rest of the group. This was likely a contributing factor to their long term survival; however, this does not explain seven years of disease-free survival. All of the patients in the trial had a KPS  $\geq 70$  and the median KPS was 80.

TTField therapy has been shown to effectively inhibit glioma cell replication *in vitro* and *in vivo* [8,9]. The published results of the pilot trial using TTField therapy in GBM patients were extremely promising and served as the basis for a phase III clinical trial comparing TTField therapy to the best available active chemotherapy in patients with RGBM [11]. The phase III trial showed that patients with RGBM had comparable overall survival to those receiving chemotherapy without the side effects of chemotherapy and with a better quality of life. In the present study, no serious, probable, treatment-related adverse events occurred, with only contact dermatitis treated by topical corticosteroid documented in 17 of 20 patients. In the phase III trial, 8% of TTField therapy patients survived for longer than three years [11]. The reasons for the smaller number of long term survival patients in the phase III trial compared to the pilot trial is likely related to the younger age of the





patients presented in this report, the fact that they were at their first recurrence after temozolomide (versus second to third recurrence in the phase III trial) and, most importantly, continued TTField therapy for many months, despite initial growth of the contrast enhancing lesion while on therapy. Thus, we suggest that in order to increase the probability of response to TTField therapy and subsequent long term survival, TTField treatment should be continued even in the face of initial radiologic tumor growth.

## Conclusions

In the present paper we report two cases of GBM and two cases of RGBM treated by TTField therapy, all in good health and no longer receiving any treatment more than seven years after initiating TTField therapy, with no clinical or radiological evidence of recurrence. Our results indicate that TTField treatment may be remarkably successful in a subgroup of GBM/RGBM patients, and further investigation is needed to identify any unique characteristics of this patient group.

## Consent

Written informed consent was obtained from all patients for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

## Abbreviations

BOLD-fMRI: Blood oxygen level dependent functional magnetic resonance imaging; FLAIR: Fluid Attenuated Inversion Recovery; GBM: Glioblastoma multiforme; KPS: Karnofsky performance scale; LTS: Long-term survival; MRI: Magnetic resonance imaging; PET: Positron emission tomography; RGBM: Recurrent glioblastoma multiforme; TTField: Tumor-treating fields; WHO: World Health Organization.

## Competing interests

JV, JS, VD and FT are consultants for NovoCure, Ltd, Haifa, Israel. AMR, JiK, JaK and MS have no competing interests to declare.

## Authors' contributions

JV participated in conception and design of the manuscript; acquisition, analysis and interpretation of the data; initial drafting and revision of the manuscript; and approval of the final version. AMR participated in conception and design of the manuscript, drafting and revision of the manuscript, preparation of images and approval of the final version. JiK participated in conception and design of the manuscript, drafting and revision of the manuscript and approval of final version. JaK, JS, VD, MS and FT participated in the acquisition, analysis and interpretation of the data, revision of the manuscript and approval of the final version. All authors read and approved the final manuscript.

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## Reprint Article

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### Preliminary Communication

# Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma A Randomized Clinical Trial

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## Preliminary Communication

# Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma

## A Randomized Clinical Trial

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**IMPORTANCE** Glioblastoma is the most devastating primary malignancy of the central nervous system in adults. Most patients die within 1 to 2 years of diagnosis. Tumor-treating fields (TTFields) are a locoregionally delivered antimitotic treatment that interferes with cell division and organelle assembly.

**OBJECTIVE** To evaluate the efficacy and safety of TTFields used in combination with temozolomide maintenance treatment after chemoradiation therapy for patients with glioblastoma.

**DESIGN, SETTING, AND PARTICIPANTS** After completion of chemoradiotherapy, patients with glioblastoma were randomized (2:1) to receive maintenance treatment with either TTFields plus temozolomide (n = 466) or temozolomide alone (n = 229) (median time from diagnosis to randomization, 3.8 months in both groups). The study enrolled 695 of the planned 700 patients between July 2009 and November 2014 at 83 centers in the United States, Canada, Europe, Israel, and South Korea. The trial was terminated based on the results of this planned interim analysis.

**INTERVENTIONS** Treatment with TTFields was delivered continuously (>18 hours/day) via 4 transducer arrays placed on the shaved scalp and connected to a portable medical device. Temozolomide (150-200 mg/m<sup>2</sup>/d) was given for 5 days of each 28-day cycle.

**MAIN OUTCOMES AND MEASURES** The primary end point was progression-free survival in the intent-to-treat population (significance threshold of .01) with overall survival in the per-protocol population (n = 280) as a powered secondary end point (significance threshold of .006). This prespecified interim analysis was to be conducted on the first 315 patients after at least 18 months of follow-up.

**RESULTS** The interim analysis included 210 patients randomized to TTFields plus temozolomide and 105 randomized to temozolomide alone, and was conducted at a median follow-up of 38 months (range, 18-60 months). Median progression-free survival in the intent-to-treat population was 7.1 months (95% CI, 5.9-8.2 months) in the TTFields plus temozolomide group and 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide alone group (hazard ratio [HR], 0.62 [98.7% CI, 0.43-0.89]; P = .001). Median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTFields plus temozolomide group (n = 196) and 15.6 months (95% CI, 13.3-19.1 months) in the temozolomide alone group (n = 84) (HR, 0.64 [99.4% CI, 0.42-0.98]; P = .004).

**CONCLUSIONS AND RELEVANCE** In this interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival.

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**G**lioblastoma is the most devastating primary malignancy of the central nervous system in adults. Standard treatment consists of maximal safe surgical resection or a diagnostic biopsy, followed by radiotherapy (60 Gy) with concomitant daily temozolomide chemotherapy, and then maintenance treatment with temozolomide for 6 to 12 months.<sup>1</sup> However, most patients will die within 1 to 2 years. Median progression-free survival from diagnosis of 6.2 to 7.5 months and median overall survival from diagnosis of 14.6 to 16.7 months have been reported in clinical trials.<sup>1-4</sup> The reported 2- and 5-year survival rates<sup>5</sup> are 27% and 10%, respectively. During the last decade, all attempts to improve the outcome for patients with glioblastoma have failed when evaluated in large randomized trials.<sup>2-4,6,7</sup>

Tumor-treating fields (TTFields) are an antimitotic treatment that selectively disrupts the division of cells by delivering low-intensity, intermediate-frequency (200 kHz) alternating electric fields via transducer arrays applied to the shaved scalp.<sup>8-10</sup> In preclinical models, TTFields have been shown to cause mitotic arrest and apoptosis by disrupting mitotic spindle formation during metaphase and causing dielectrophoretic movement of polar molecules during cytokinesis.<sup>8,10-12</sup> In a randomized phase 3 trial in which TTFields were compared with chemotherapy in 237 patients with recurrent glioblastoma, the use of TTFields did not prolong progression-free survival or overall survival, but the therapy was associated with better quality of life without the typical chemotherapy-associated toxic effects.<sup>13</sup>

Based on preclinical data demonstrating a synergistic antitumor effect with chemotherapy and TTFields, and pilot clinical feasibility data in combination with temozolomide,<sup>9</sup> we initiated this phase 3 trial. The objective was to evaluate the efficacy and safety of TTFields used in combination with maintenance temozolomide in patients with glioblastoma after initial treatment with temozolomide and radiotherapy.

## Methods

### Study Population

Patients eligible for this study (1) had histologically confirmed supratentorial glioblastoma (World Health Organization grade IV astrocytoma<sup>14</sup>), (2) were progression-free after having undergone maximal safe debulking surgery when feasible or biopsy, and (3) had completed standard concomitant chemoradiotherapy with temozolomide. Other eligibility criteria were (1) age of 18 years or older, (2) Karnofsky Performance Status (KPS) score of 70% or higher (the KPS score describes the general condition of a patient; a KPS score  $\geq 70\%$  ensures some independence in activities of daily living), and (3) adequate bone marrow, liver, and renal function.

Prior use of implanted carmustine wafers was allowed. Patients with infratentorial tumor location and severe comorbidities were excluded. All patients provided written informed consent before entering the study; the study was approved by the institutional review boards or ethics committees of all 83 participating centers. The trial protocol appears in Supplement 1.

### Study Design and Treatment

This multicenter, open-label, randomized phase 3 trial was designed to test the efficacy and safety of TTFields in combination with temozolomide for treatment of glioblastoma after initial treatment with chemoradiation. After the completion of treatment with temozolomide and radiotherapy, patients were randomized at a ratio of 2 to 1 (Figure 1) to receive standard maintenance temozolomide chemotherapy (150-200 mg/m<sup>2</sup>/d for 5 days every 28 days for 6-12 cycles according to the protocol<sup>1</sup> from the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group) with or without the addition of TTFields. Treatment with TTFields was to be initiated within 4 to 7 weeks from the last dose of concomitant temozolomide and radiotherapy. Randomization was performed through a central web-based randomization system and was stratified by extent of resection (biopsy, partial resection, gross total resection) and by O<sup>6</sup>-methylguanine-DNA methyltransferase (*MGMT*) methylation status (methylated, unmethylated, or unknown).

For patients with available paraffin-embedded tumor tissue, evaluation of *MGMT* gene promoter methylation status was performed as described previously<sup>7,15,16</sup> by a central laboratory blinded to treatment group (MDxHealth). If *MGMT* methylation status could not be determined centrally prior to randomization, local *MGMT* methylation status was used for stratification.

Patients in the TTFields plus temozolomide group received continuous TTFields combined with standard maintenance temozolomide. Patients receiving TTFields had 4 transducer arrays placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain (Optune, Novocure Ltd). Transducer array layouts were determined using a mapping software system for TTFields to optimize field intensity within the treated tumor (NovoTAL, Novocure Ltd). After being trained to operate the device, the patient continued treatment at home. The transducer arrays were supplied in sterile packaging and replaced by the patient, a caregiver, or a device technician twice per week. Although uninterrupted treatment was recommended, short treatment breaks for personal needs were allowed.

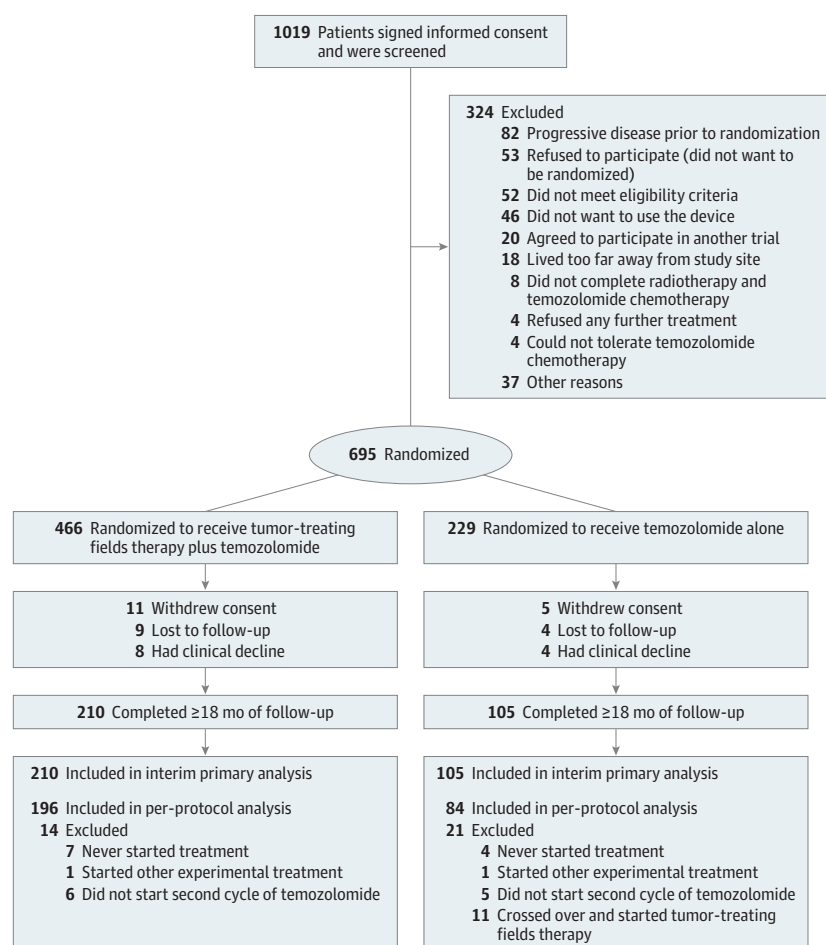
If a patient experienced tumor progression, second-line chemotherapy was offered per local practice. However, in the TTFields plus temozolomide group, TTFields could be continued until the second radiological progression, or clinical deterioration, for a maximum of 24 months.

### Patient Surveillance and Follow-up

Baseline contrast-enhanced magnetic resonance imaging (MRI) of the brain was required within 2 weeks before starting treatment with maintenance temozolomide with or without TTFields. A complete physical examination with collection of laboratory parameters was performed within 1 week of treatment initiation. The evaluation also included a quality-of-life questionnaire (QLQ-C30) that has a brain-specific module (BN-20), which was developed by the European Organisation



Figure 1. Recruitment and Inclusion of Patients in the Study



for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups.<sup>17,18</sup> A Mini-Mental State Examination (a short bedside test used to evaluate cognition and memory) also was administered (a test result of 27-30 points is considered normal function).

Patients were seen monthly for medical follow-up and routine laboratory examinations. Quality of life was assessed every 3 months. Magnetic resonance imaging was to be performed every second month after the baseline MRI until second radiological progression in all patients. In the event of clinical progression, MRI was to be performed within 1 week after the study investigator became aware of it. All MRIs were reviewed centrally by 2 blinded independent radiologists (BioClinica Inc) and were evaluated for tumor response and progression using the criteria developed by Macdonald et al.<sup>19</sup> In cases in which the central reviewers were not in agreement, a third blinded radiologist adjudicated between them. The third radiologist was involved in 17% of the cases in the TTFields plus temozolomide group and in 18% of the cases in the temozolomide alone group.

The results of the central review were not communicated to the study investigator, and all treatment decisions were based on local imaging interpretation. Eight patients in the

TTFields plus temozolomide group (4%) compared with 6 patients in the temozolomide alone group (3%) were considered stable by blinded central review; however, treatment had been changed by the study investigator due to local interpretation of tumor progression. Patients were removed from the progression-free survival analysis at the date of treatment change when this occurred before evidence of tumor progression or when patients reached the cutoff date without tumor progression.

Adverse events were recorded prospectively according to the National Cancer Institute's Common Terminology Criteria (version 3.0) until 2 months after treatment discontinuation. Adverse events are presented descriptively as number and percentage of patients with each adverse event term for all patients available at the time of the interim analysis. Treatment adherence with TTFields was recorded electronically by the device as average daily use in hours per day and information was reviewed and transferred at the monthly follow-up visit.

### Statistical Considerations

The primary end point was progression-free survival in the intent-to-treat (ITT) population assessed by an independent review panel (80% power; hazard ratio [HR], 0.78; 2-sided  $\alpha$  level



of .05). The study was also designed to have 80% power (HR, 0.76; 2-sided a level of .05) to examine overall survival as a secondary end point. To avoid an increase in the risk of a false-positive result, overall survival was to be tested statistically only if the primary end point was met.

This prespecified interim analysis was to be performed after the first 315 randomized patients reached a minimum 18-month follow-up. The final type I error rate of 0.05 was split between the interim and final analyses based on a standard a spending function.<sup>20-22</sup> The protocol prespecified that overall survival would be analyzed in an as-treated population, excluding all patients in both treatment groups who (1) never started maintenance temozolomide, (2) had major protocol violations, (3) crossed over to the other treatment group, or (4) received TTFields outside the protocol setting.

The primary end point would be achieved in the interim analysis if progression-free survival in the ITT population was significantly longer in the intervention group compared with the control group using a stratified log-rank test with an a level of .01. The secondary end point would be achieved in the interim analysis if overall survival in the as-treated population (per-protocol population) was significantly longer in the TTFields plus temozolomide group using a stratified log-rank test with an a level of .006. The confidence intervals that go with the HRs are presented as 1 minus the prespecified a level for each analysis. For example, the a level in the per-protocol interim analysis for overall survival was .006. Therefore, the corresponding confidence interval used for presenting the HRs was 1.000 – 0.006 (99.4% confidence interval). An upper confidence limit of less than 1 indicates the prespecified statistical threshold was met. An independent data and safety monitoring committee was chartered to stop the trial if the interim analysis of progression-free survival (ITT population) and overall survival (per-protocol population) surpassed these predetermined thresholds, as well as for futility or safety concerns.

In addition to these prespecified analyses, an analysis of overall survival in the ITT population was performed. Furthermore, a robustness analysis including all 695 patients enrolled in the trial served to validate the findings of the interim analysis (database lock: December 29, 2014; eAppendix 1 in Supplement 2).

Multiple imputation analyses also were performed for the trial's primary end point of progression-free survival in the ITT population to test the sensitivity of the results to possible bias using informative and interval censoring. These analyses included (1) treating all patients with informative censoring as treatment failures in the TTFields plus temozolomide group, (2) censoring all patients with informative censoring in the temozolomide alone group (worst case scenario), and (3) treating all events in the TTFields plus temozolomide group and in the temozolomide alone group as occurring differentially at different periods during the inter-MRI interval before the date of tumor progression.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) and R version 3.1.1.<sup>23</sup> The final analysis will be performed when all 695 patients enrolled in the study have at least 18 months of follow-up and will include prespeci-

fied subgroup analyses and additional secondary end points, including quality of life.

## Results

### Study Participants

Between July 2009 and November 2014, there were 695 patients with newly diagnosed glioblastoma randomized to receive either TTFields plus temozolomide (n = 466) or temozolomide alone (n = 229). Data for the interim analysis included 210 patients randomized to TTFields plus temozolomide and 105 to temozolomide alone (Figure 1; database lock: September 5, 2014). The independent data and safety monitoring committee met in October 2014 to review the interim analysis; the trial met the predefined boundaries for success (improvement of both progression-free and overall survival) and the committee recommended study termination, thus allowing patients in the control group to crossover and receive TTFields.

After approval of study termination by the US Food and Drug Administration, the trial was closed to recruitment on November 29, 2014, after 695 patients of the planned 700 patients had already been randomized. All patients in the control group with ongoing maintenance therapy were offered to receive TTFields. At the time of this report, 35 patients in the control group crossed over to receive TTFields. Follow-up for all patients continues according to the protocol.

Patient baseline characteristics were well balanced between the 2 groups (Table 1). The median age was 57 years and 66% were male. The median KPS score was 90%. Sixty-four percent of patients had a gross total resection and 11% had only a diagnostic biopsy. Tumor tissue for central *MGMT* testing was available for 72% of the patients; the *MGMT* methylation frequency was 39% (75/191 valid tests; 39% for the TTFields plus temozolomide group and 41% for the temozolomide alone group). Tumor location in the brain was also comparable.

Carmustine wafers (Gliadel) were used at initial surgery in 2.4% of patients in the TTFields plus temozolomide group vs 2.9% of patients in the temozolomide alone group. Ninety-five percent of the patients were white and 61% were treated in the United States. The rest of the patients were treated at centers in Canada, Europe, Israel, and South Korea. The median time from diagnosis to randomization was 3.8 months (range, 2.0-5.7 months) for patients in the TTFields plus temozolomide group and 3.8 months (range, 1.4-5.7 months) for those in the temozolomide alone group. The median time from the end of treatment with temozolomide and radiotherapy to randomization was 36 days in the TTFields plus temozolomide group and 38 days in the temozolomide alone group; 53% of patients were randomized after having started the first cycle of maintenance temozolomide. The median time from randomization to initiation of TTFields was 5 days.

### Treatment Delivery

All patients had completed radiotherapy and concomitant temozolomide as per local practice. The median number of temozolomide cycles until evidence of first tumor progression was 6 cycles (range, 1-26 cycles) for patients in the TTFields



Table 1. Patient Baseline Characteristics and Treatment Details

	All Patients (N = 315)	TTFields Plus Temozolomide (n = 210)	Temozolomide Alone (n = 105)
Age, y			
Mean (SD)	55.8 (11.1)	55.3 (11.3)	56.8 (10.5)
Median (range)	57 (20-83)	57 (20-83)	58 (21-80)
Karnofsky Performance Status score, median (range), % <sup>a</sup>	90 (60-100)	90 (60-100)	90 (70-100)
Sex, No. (%)			
Male	207 (66)	140 (67)	67 (64)
Female	108 (34)	70 (33)	38 (36)
Use at baseline, No. (%)			
Antiepileptic medication	126 (40)	88 (42)	38 (36)
Corticosteroid therapy	77 (24)	51 (24)	26 (25)
Mini-Mental State Examination score, No. (%) <sup>b</sup>			
≤26	45 (15)	31 (15)	14 (13)
27-30	247 (78)	174 (83)	73 (70)
Unknown	23 (7)	5 (2)	18 (17)
Extent of resection, No. (%)			
Biopsy	34 (11)	23 (11)	11 (10)
Partial resection	79 (25)	52 (25)	27 (26)
Gross total resection	202 (64)	135 (64)	67 (64)
Tissue available and tested, No. (%)			
MGMT methylation	75 (33)	49 (32)	26 (35)
No methylation	116 (51)	79 (52)	38 (51)
Invalid test result	36 (16)	24 (16)	11 (15)
Region, No. (%)			
United States	191 (61)	127 (60)	64 (61)
Rest of world	124 (39)	83 (40)	41 (39)
Completed radiation therapy, No. (%)			
<57 Gy	18 (6)	13 (6)	5 (5)
60 Gy (standard; ±5%)	291 (92)	191 (91)	100 (95)
>63 Gy	6 (2)	6 (3)	0 (0)
Concomitant temozolomide use, No. (%)			
Yes	308 (98)	207 (99)	101 (96)
Unknown	7 (2)	3 (1)	4 (4)
Time from event to randomization, median (range), d			
Last day of radiotherapy	37 (13-68)	36 (13-53)	38 (13-68)
Initial diagnosis	114 (43-171)	115 (59-171)	113 (43-170)
No. of maintenance temozolomide cycles until first tumor progression, median (range)	6 (1-26)	6 (1-26)	4 (1-24)
Duration of treatment with TTFields, median (range), mo	9 (1-58)	9 (1-58)	
Adherence to TTFields therapy ≥75% during first 3 mo of treatment		157 (75)	

Abbreviations: MGMT, O<sup>6</sup>-methylguanine-DNA methyltransferase; TTFields, tumor-treating fields.

<sup>a</sup> A higher score indicates better functional status.

<sup>b</sup> A higher score indicates better cognitive capability.

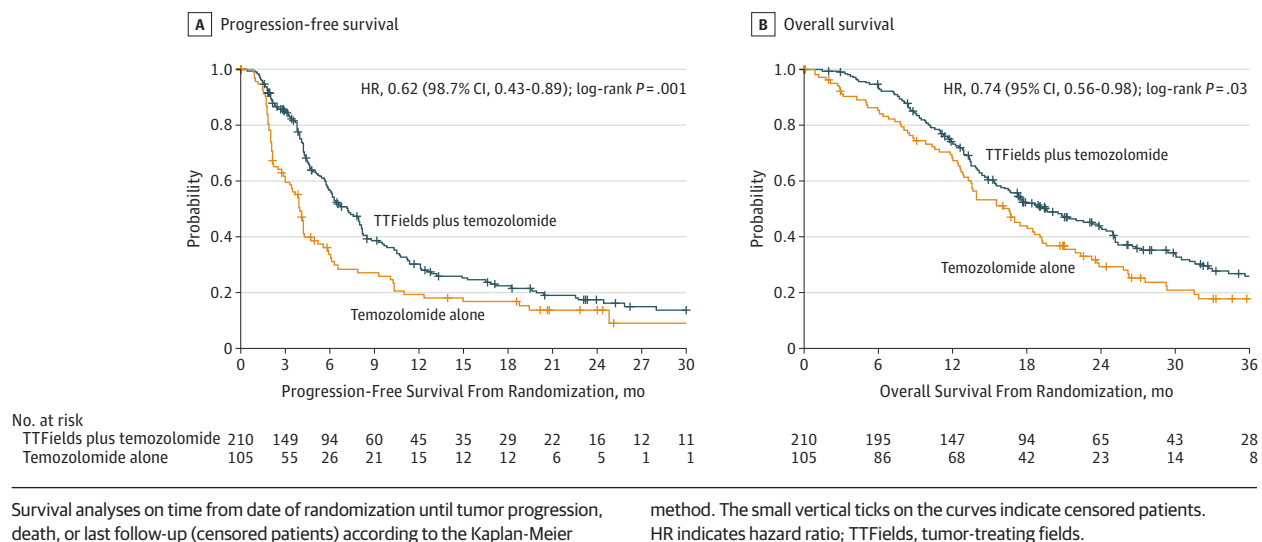
plus temozolomide group and 4.0 cycles (range, 1-24 cycles) for patients in the temozolomide alone group; the median duration of treatment with TTFields was 9 months (range, 1-58 months). Two-thirds (n = 141) of patients in the TTFields plus temozolomide group continued treatment with TTFields after first tumor progression. Three-quarters (n = 157) of patients receiving treatment with TTFields were adherent to therapy (ie, wearing the device >18 hours per day on average during the first 3 treatment months).

### Efficacy End Points

As prespecified, the primary end point for the efficacy results was based on progression-free survival in the ITT population of the interim analysis data set. After a median follow-up of 38 months (range, 18-60 months), the median progression-free survival from randomization was 7.1 months (95% CI, 5.9-8.2 months) in the TTFields plus temozolomide group compared with 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide alone group (HR, 0.62 [98.7% CI, 0.43-0.89];



Figure 2. Survival Curves for Patients Included in the Interim Analysis in the Intent-to-Treat Population



stratified log-rank  $P = .001$ ; **Figure 2A**). Thus, adding TTFields to temozolomide treatment increased median progression-free survival in the ITT population by 3.1 months.

As per the statistical analysis plan, overall survival was to be tested in a prespecified per-protocol population only after the primary end point was found to surpass the threshold for significance in the interim analysis. Median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTFields plus temozolomide group ( $n = 196$ ) compared with 15.6 months (95% CI, 13.3-19.1 months) in the temozolomide alone group ( $n = 84$ ) (HR, 0.64 [95% CI, 0.42-0.98]; stratified log-rank  $P = .004$ ). The details on the per-protocol population and analyses are summarized in eAppendix 2 in Supplement 2.

In additional analyses in the ITT population, the median overall survival was 19.6 months (95% CI, 16.6-24.4 months) in the TTFields plus temozolomide group compared with 16.6 months (95% CI, 13.6-19.2 months) in the temozolomide alone group (HR, 0.74 [95% CI, 0.56-0.98]; stratified log-rank  $P = .03$ ; **Figure 2B**). The percentage of patients alive at 2 years following enrollment was 43% in the TTFields plus temozolomide group and 29% in the temozolomide alone group ( $P = .006$ ).

To assess the robustness of the interim analysis findings, additional analyses on all 695 patients randomized were performed. Patient characteristics of all patients randomized did not differ significantly from the interim data set, and the results for the main end points were similar in these analyses compared with the interim analysis (eAppendix 1 in Supplement 2).

Second-line treatments, such as nitrosoureas, temozolomide rechallenge, and bevacizumab, were received by 67% of the patients in the TTFields plus temozolomide group compared with 57% in the temozolomide alone group; about 40% of second-line therapies included bevacizumab and about 40% included nitrosoureas. The type of chemotherapy used at recurrence was balanced between treatment groups.

Secondary imputation analyses of progression-free survival with relation to the effects of interval and informational censoring did not change the conclusions of the primary progression-free survival analysis (eAppendix 3 in Supplement 2).

### Safety and Tolerability

The addition of TTFields to temozolomide therapy in patients with newly diagnosed glioblastoma was not associated with any significant increase in systemic toxic effects compared with temozolomide therapy alone (**Table 2**). The overall incidence, distribution, and severity of adverse events were similar in patients treated with TTFields plus temozolomide and in those treated with temozolomide alone. The only notable exception was a higher incidence rate of localized skin toxicity (medical device site reaction beneath the transducer arrays) in patients treated with TTFields plus temozolomide. Mild to moderate skin irritation was observed in 43% of patients treated with TTFields plus temozolomide and severe skin reaction (grade 3) in 2%. Mild anxiety, confusion, insomnia, and headaches were reported more frequently in the patients treated with TTFields plus temozolomide and occurred mainly at the time of therapy initiation. The incidence of seizures was almost identical in the 2 groups (15 [7%] in the TTFields plus temozolomide group vs 8 [8%] in temozolomide alone group). A total of 12 patients died of causes considered unrelated to treatment while receiving adjuvant therapy (8 [3.9%] in the temozolomide plus TTFields group and 4 [4.0%] in the temozolomide alone group; **Table 2**).

### Discussion

Glioblastoma is a highly aggressive brain tumor affecting men and women, frequently at the peak of life. Prognosis remains poor with no major treatment advance in more than a decade. In the interim analysis of this randomized clinical trial,



the addition of TTFields to standard maintenance temozolomide significantly improved progression-free and overall survival. The prespecified analyses revealed that patients randomized to receive TTFields plus temozolomide compared with patients randomized to receive temozolomide alone had a median progression-free survival of 7.1 months vs 4.0 months (ITT analyses). Patients who received TTFields plus temozolomide had a median overall survival of 20.5 months compared with 15.6 months in those who received temozolomide alone (as per the prespecified per-protocol analysis; the ITT analysis did not differ substantially).

Based on the results of this planned interim analysis, the trial's independent data and safety monitoring committee recommended termination of the trial. Because almost all patients had been enrolled (695/700) in the study by the time the recommendation was implemented, the full trial population will be followed up for both progression-free and overall survival. Subsequent analyses of all secondary end points and subgroups will be performed when the follow-up data are available.

The trial population and the results in the control group in this study were comparable with other glioblastoma clinical trials. Nevertheless, patients in this trial were randomized only after the end of radiochemotherapy, and for most, the first cycle of maintenance temozolomide had been started at the time of randomization; thus, patients with early tumor progression during radiochemotherapy were excluded. Most glioblastoma trials have reported survival from the date of initial diagnosis or study enrollment before starting radiochemotherapy, thus 3 to 4 months before randomization of the current study.

When the interval from diagnosis to randomization is added to the outcome results in this study, the progression-free survival of 7.8 months in the control group is comparable with most other reported studies, and supports the generalizability of these results. The Radiation Therapy Oncology Group (RTOG) 0525 protocol randomized patients only after the end of treatment with temozolomide and radiotherapy, similar to our study.<sup>3</sup> The control groups with standard dose temozolomide only in these 2 trials were comparable: progression-free survival from randomization of 4.0 months in the present study and 5.5 months in the RTOG 0525 trial and overall survival of 16.6 months in both trials. Thus, the benefit observed with TTFields cannot be simply attributed to patient selection. In the present trial, the gain of 3 months in both median progression-free survival (from 4.0 months to 7.2 months; HR, 0.62) and median overall survival (from 16.6 months to 19.6 months; HR, 0.74), translating into a survival gain at 2 years of 14% (from 29% to 43%) in the ITT population is in the range of benefit that is considered clinically meaningful for therapeutic agents in oncology.

The prespecified analysis for overall survival in the interim analysis was to be based on the per-protocol population (n = 280); ie, removal in both study groups of the patients who did not start their second course of maintenance temozolomide or had major protocol violations. This analysis met the prespecified threshold for efficacy in the interim analysis for the per-protocol population. In a more conserva-

Table 2. Grade 3 to 4 Treatment-Emergent Adverse Events

	No. (%) of Patients With Adverse Events <sup>a</sup>	
	TTFields Plus Temozolomide (n = 203) <sup>b</sup>	Temozolomide Alone (n = 101) <sup>c</sup>
Hematological disorders <sup>d</sup>	25 (12)	9 (9)
Anemia	1 (<1)	2 (2)
Leukopenia or lymphopenia	11 (5)	5 (5)
Neutropenia	6 (3)	1 (1)
Thrombocytopenia	19 (9)	3 (3)
Cardiac disorders	2 (1)	3 (3)
Eye disorders	2 (1)	1 (1)
Gastrointestinal disorders <sup>d</sup>	11 (5)	2 (2)
Abdominal pain	2 (1)	0
Constipation	2 (1)	0
Diarrhea	1 (<1)	2 (2)
Vomiting	3 (1)	1 (1)
General disorders	17 (8)	5 (5)
Fatigue	8 (4)	4 (4)
Infections	10 (5)	5 (5)
Injury and procedural complications <sup>d</sup>	14 (7)	5 (5)
Fall	6 (3)	2 (2)
Medical device site reaction	4 (2)	0
Metabolism and nutrition disorders	7 (3)	3 (3)
Musculoskeletal disorders	8 (4)	3 (3)
Nervous system disorders <sup>d</sup>	45 (22)	25 (25)
Seizure	15 (7)	8 (8)
Headache	4 (2)	2 (2)
Psychiatric disorders <sup>d</sup>	9 (4)	3 (3)
Anxiety	2 (1)	0
Bradyphrenia	0	1 (1)
Confusional state	2 (1)	1 (1)
Mental status changes	4 (2)	1 (1)
Psychotic disorder	2 (1)	0
Respiratory disorders	4 (2)	1 (1)
Skin disorders	0	1 (1)
Vascular disorders <sup>d</sup>	8 (4)	8 (8)
Deep vein thrombosis	1 (<1)	3 (3)
Pulmonary embolism	4 (2)	6 (6)

Abbreviation: TTFields, tumor-treating fields.

<sup>a</sup> Safety is reported on patients who have received any treatment. Randomized patients who never received any maintenance therapy were excluded from this safety analysis.

<sup>b</sup> Eight patients died while receiving adjuvant therapy due to causes unrelated to therapy (1 patient for each of the following reasons: cardiac events, pulmonary emboli, respiratory, and infection; and 4 patients with central nervous system disorders likely due to tumor progression).

<sup>c</sup> Four patients died while receiving adjuvant therapy due to causes unrelated to therapy (1 patient for each of the following reasons: cardiac events, pulmonary emboli, respiratory, and unknown).

<sup>d</sup> Patients may have had more than 1 adverse event so subcategories do not total and not all events are subcategorized.

tive analysis using the ITT population, an overall survival benefit was also manifest. Furthermore, an analysis of robustness performed on all randomized patients enrolled at the time



of study termination (eAppendix 1 in Supplement 2) supports the conclusions of the interim analysis.

This clinical trial has some important limitations. Patient enrollment occurred only after the end of radiochemotherapy, leading to some variation in the delivery of standard treatment of temozolomide and radiotherapy. Patients who had progressed early during radiochemotherapy were not eligible for randomization, thus excluding patients with very poor prognoses. There is likely reporting bias for second-line therapies after tumor progression because in the TTFields plus temozolomide group, TTFields were to be continued, and thus, more detailed treatment information has been tracked for this group.

This analysis reports a planned interim analysis on data from the first 315 patients with at least 18 months of follow-up; however, for detailed and meaningful subgroup analyses, the mature data of the full data set will be needed. Treatment failure patterns, effects of second-line therapies, and additional molecular analyses on baseline tumor biopsies will allow for better understanding of the clinical effects of this novel treatment modality. With the last patient randomized on November 29, 2014, however, these data are not expected before the end of 2016.

This was an open-labeled study. A sham or placebo treatment for the control group was considered neither practical (patients would be able to sense heat when they were receiving TTFields) nor appropriate (due to the burden for patients and caregivers and the need to shave the scalp and have transducer arrays placed). In this respect, the trial resembles studies evaluating radiation therapy. This raises the question of a placebo effect leading to the improved outcome. Although some effect of placebo may be expected on subjective end points, such as cognitive function and quality of life, objective end points, such as overall and progression-free survival (assessed by a blinded review panel), are independent of pla-

cebo effects in cancer therapy.<sup>24</sup> The panel did not have information on treatment received and no stigmata of TTFields array pads were evident on MRI.

Recent randomized studies of patients with glioblastoma, which did not use placebo controls, failed to show any increase in progression-free or overall survival<sup>3,7</sup> despite intensive treatment regimens requiring twice weekly hospital visits.<sup>7</sup> The magnitude of effect size seen in the present trial (HR of 0.62 for progression-free survival and 0.74 for overall survival) is beyond what could be attributed to a placebo effect. In addition, the support provided to patients in the TTFields plus temozolomide group by device support specialists during the trial was largely technical in nature and did not include medical supportive care. Medical follow-up with monthly visits was the same for both treatment groups.

Because TTFields were applied only to the head, an increase in systemic adverse events was neither seen nor expected. No increase in seizure rate or neurological adverse events was observed. Almost half of the patients treated with TTFields did experience some grade 1 to 2 (mild to moderate) localized skin reaction related to the application of the transducer arrays used to deliver the TTFields. This adverse effect could be managed using published skin care guidelines for patients receiving TTFields.<sup>25</sup> Only 2% of patients receiving TTFields had grade 3 to 4 (severe) skin reactions beneath the transducer arrays.

## Conclusions

In this interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival.

### ARTICLE INFORMATION

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New Jersey Neuroscience Institute, Edison (Landolfi); Maine Medical Center, Portland (Desai); Fondazione Ospedale Maggiore Policlinico, Milan, Italy (Caroli); Houston Methodist Hospital, Houston, Texas (Kew); Hospices Civils de Lyon, University Claude Bernard Lyon 1, Lyon, France (Honnorat); Novocure, Haifa, Israel (Kirson, Weinberg, Palti).

**Author Contributions:** Drs Stupp and Ram had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Stupp, Kirson, Weinberg, Palti, Ram.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Stupp, Kirson, Ram.

**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Steinberg.

**Obtained funding:** Palti.

**Administrative, technical, or material support:**

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**Study supervision:** Stupp, Kirson, Weinberg, Hegi, Ram.

**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for

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oncology officer in Pharmo-kinesis; and receiving grant funding, personal fees, nonfinancial support, and being a stock holder in and CEO of NeOnc Technologies. Dr David Tran reported receiving grant funding from Celldex, NWBiotech, Novocure, and Merck; and receiving personal fees from Novocure and prIme Oncology. Dr Hottinger reported receiving travel reimbursement and speakers fees from Novocure and Merck Sharp & Dohme; and receiving personal fees for serving on an advisory board for Roche. Dr Landolfi reported receiving personal fees from Novocure for serving on an advisory board. Dr Honnorat reported receiving trial support from Novocure and serving on an advisory board for Novocure. Dr Idbaih reported receiving grants from Fondation ARC pour la recherche sur le Cancer; receiving research support from IntselChimos and Beta-Innov; receiving personal fees from Novartis for attending a conference; receiving travel reimbursement from Hoffmann-La Roche; and serving as an editorial advisory board member for *Lettre du Cancérologue*. Drs Kirson, Weinberg, and Palti reported being employees of Novocure. Dr Palti also reported holding 35 issued US patents and minority stock ownership in Novocure. Dr Hegi reported receiving institutional grant funding from Novocure, Merck Sharp & Dohme, Roche, and Merck-Serono; and nonfinancial support from MDxHealth for sample testing. Dr Ram reported receiving institutional grant funding from Novocure; and serving as a paid consultant for and holding stock options in Novocure. Drs Taylor, Silvani, Barnett, Henson, Sroubek, Nam Tran, Desai, Caroli, and Kew reported having no disclosures.

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**Role of the Funder/Sponsor:** Novocure Ltd had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The study was designed by the first and last authors (R.S. and Z.R.), together with representatives from Novocure (mainly E.D.K.). The study oversight was supported and monitored by a clinical research organization (CRO), who also holds the database. Data were collected by the investigators and monitored by the CRO. Device use data were downloaded monthly and transferred to the study investigators or their research staff by device support specialists from Novocure Ltd. The data were analyzed separately by the statistician of the independent data monitoring committee and the study statistician (D.M.S.). Data interpretation was the responsibility of the first and last authors (R.S. and Z.R.), together with the study sponsor representative and project lead (E.D.K.). These 3 physicians also jointly developed the first draft. A subsequent mature draft and a prefinal version were circulated among all authors who gave additional input, contributed to, and approved the manuscript. The first and last authors (R.S. and Z.R.) and E.D.K. had full access to all data, and also reviewed all patient profiles for consistency (R.S. and E.D.K.). The decision to publish the data followed the independent data and safety monitoring committee recommendation for data release, and was supported by all coauthors.

The roles of employees of Novocure are described in the respective author contributions. Other employees' involvement was limited to technical support of the device.

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## Indications For Use and Safety Information in the United States:

Please visit [www.optune.com/IFU](http://www.optune.com/IFU) for Optune Instructions For Use (IFU) for complete information regarding the device's indications, contraindications, warnings and precautions.

Optune is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM).

Optune with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery, and completion of radiation therapy together with concomitant standard of care chemotherapy.

For the treatment of recurrent GBM, Optune is indicated following histologically- or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

### Summary of Important Safety Information

#### Contraindications

Do not use Optune in patients with an active implanted medical device, a skull defect (such as, missing bone with no replacement), or bullet fragments. Use of Optune together with implanted electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device. Use of Optune together with skull defects or bullet fragments has not been tested and may possibly lead to tissue damage or render Optune ineffective.

Do not use Optune in patients that are known to be sensitive to conductive hydrogels. In this case, skin contact with the gel used with Optune may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

#### Warnings and Precautions

Optune can only be prescribed by a healthcare provider that has completed the required certification training provided by Novocure (the device manufacturer).

Do not prescribe Optune for patients that are pregnant, you think might be pregnant or are trying to get pregnant, as the safety and effectiveness of Optune in these populations have not been established.

The most common ( $\geq 10\%$ ) adverse events involving Optune in combination with temozolomide were thrombocytopenia, nausea, constipation, vomiting, fatigue, medical device site reaction, headache, convulsions, and depression.

Use of Optune in patients with an inactive implanted medical device in the brain has not been studied for safety and effectiveness, and use of Optune in these patients could lead to tissue damage or lower the chance of Optune being effective.

If the patient has an underlying serious skin condition on the scalp, evaluate whether this may prevent or temporarily interfere with Optune treatment.

## Indications for use and safety information in Europe:

### Newly diagnosed GBM

Optune is intended for the treatment of patients with newly diagnosed GBM, after surgery and radiotherapy with adjuvant temozolomide, concomitant to maintenance temozolomide. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after surgery and radiation therapy with adjuvant temozolomide. Treatment may be given together with maintenance temozolomide (according to the prescribing information in the Temodar package insert) and after maintenance temozolomide is stopped.

### Recurrent GBM

Optune is intended for the treatment of patients with recurrent GBM who have progressed after surgery, radiotherapy and temozolomide treatment for their primary disease. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after the latest surgery, radiation therapy or chemotherapy.

#### Contraindications

Do not use Optune if you are pregnant, think you might be pregnant, or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. Optune was not tested in pregnant women. Do not use Optune if you have clinically significant hepatic, renal or hematologic disease. Do not use Optune if you have significant additional neurological disease (primary seizure disorder, dementia, progressive degenerative neurological disorder, meningitis or encephalitis, hydrocephalus associated with increased intracranial pressure). Do not use Optune if you are known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with Optune Treatment Kit may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

#### Warnings and Precautions

Use Optune only after receiving training from qualified personnel, such as your doctor, a nurse, or other medical personnel who have completed a training course given by the device manufacturer (Novocure). All servicing procedures must be performed by qualified and trained personnel.

Do not use Optune Treatment Kit if you are 17 years old or younger. The system has not been tested in persons 17 years old or younger. It is unknown what side effects the device may cause in these cases or if it will be effective.

Do not wet the device or the transducer arrays. Do not use any parts that do not come with the Optune treatment kit, or that were not sent to you by the device manufacturer or given to you by your doctor.

Optune commonly causes skin irritation beneath the transducer arrays and in rare cases lead to headaches, falls, fatigue, muscle twitching or skin ulcers.

For complete information regarding Optune's indication, contraindication, warnings and precautions please see the [Instructions for Use \(IFU\)](http://www.optune.com/deutsch/materialien/schulungen.aspx). (<http://www.optune.com/deutsch/materialien/schulungen.aspx>)



JAMA | Original Investigation

# Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma

## A Randomized Clinical Trial

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**IMPORTANCE** Tumor-treating fields (TTFields) is an antimitotic treatment modality that interferes with glioblastoma cell division and organelle assembly by delivering low-intensity alternating electric fields to the tumor.

**OBJECTIVE** To investigate whether TTFields improves progression-free and overall survival of patients with glioblastoma, a fatal disease that commonly recurs at the initial tumor site or in the central nervous system.

**DESIGN, SETTING, AND PARTICIPANTS** In this randomized, open-label trial, 695 patients with glioblastoma whose tumor was resected or biopsied and had completed concomitant radiochemotherapy (median time from diagnosis to randomization, 3.8 months) were enrolled at 83 centers (July 2009-2014) and followed up through December 2016. A preliminary report from this trial was published in 2015; this report describes the final analysis.

**INTERVENTIONS** Patients were randomized 2:1 to TTFields plus maintenance temozolomide chemotherapy (n = 466) or temozolomide alone (n = 229). The TTFields, consisting of low-intensity, 200 kHz frequency, alternating electric fields, was delivered ( $\geq 18$  hours/d) via 4 transducer arrays on the shaved scalp and connected to a portable device. Temozolomide was administered to both groups (150-200 mg/m<sup>2</sup>) for 5 days per 28-day cycle (6-12 cycles).

**MAIN OUTCOMES AND MEASURES** Progression-free survival (tested at  $\alpha = .046$ ). The secondary end point was overall survival (tested hierarchically at  $\alpha = .048$ ). Analyses were performed for the intent-to-treat population. Adverse events were compared by group.

**RESULTS** Of the 695 randomized patients (median age, 56 years; IQR, 48-63; 473 men [68%]), 637 (92%) completed the trial. Median progression-free survival from randomization was 6.7 months in the TTFields-temozolomide group and 4.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.52-0.76;  $P < .001$ ). Median overall survival was 20.9 months in the TTFields-temozolomide group vs 16.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76;  $P < .001$ ). Systemic adverse event frequency was 48% in the TTFields-temozolomide group and 44% in the temozolomide-alone group. Mild to moderate skin toxicity underneath the transducer arrays occurred in 52% of patients who received TTFields-temozolomide vs no patients who received temozolomide alone.

**CONCLUSIONS AND RELEVANCE** In the final analysis of this randomized clinical trial of patients with glioblastoma who had received standard radiochemotherapy, the addition of TTFields to maintenance temozolomide chemotherapy vs maintenance temozolomide alone, resulted in statistically significant improvement in progression-free survival and overall survival. These results are consistent with the previous interim analysis.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: [NCT00916409](https://clinicaltrials.gov/ct2/show/study/NCT00916409)

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**G**lioblastoma is the most common and aggressive primary brain tumor with an annual incidence of 3.19 per 100 000.<sup>1-5</sup> The disease course is typically rapid, with only approximately 1 in 4 patients alive 2 years after diagnosis, and only 5% to 10% of patients alive at 5 years.<sup>1,6,7</sup>

Since the current standard of care was established, consisting of surgical resection or biopsy, followed by radiotherapy with concomitant temozolomide chemotherapy, followed by maintenance temozolomide for 6 to 12 months,<sup>6</sup> little progress has been made in the treatment of this disease.<sup>3,8,9</sup> Most trials have shown median progression-free survival and median overall survival from diagnosis of 6.2 to 7.5 months and 14.6 to 16.7 months, respectively.<sup>4-6,8</sup>

Tumor-treating fields (TTFields) are an antimetabolic treatment that selectively affects dividing glioblastoma cells by delivering low-intensity, intermediate-frequency (200 kHz) alternating electric fields via transducer arrays applied to the scalp.<sup>10,11</sup> Tumor-treating fields cause mitotic arrest and apoptosis of rapidly dividing cells.<sup>10,11</sup> Preclinical studies demonstrated increased sensitivity to chemotherapy with the addition of TTFields in human glioblastoma cell lines and in animal tumor models.<sup>12</sup> In a randomized phase 3 trial involving 237 patients with recurrent glioblastoma whose several lines of prior therapy had failed, TTFields monotherapy was compared with the treating physicians' best choice of salvage chemotherapy. Although no survival difference was observed, the higher objective response rate (12% vs 7%) suggested single-modality activity of TTFields.<sup>13</sup>

In 2009, this randomized phase 3 clinical trial was initiated, comparing maintenance temozolomide alone with maintenance temozolomide in combination with TTFields among patients with glioblastoma. A preplanned interim analysis involving the first 315 patients randomized was previously reported and demonstrated improved progression-free and overall survival.<sup>14</sup> This article reports the final analysis involving all 695 randomized patients, with a median follow-up of 40 months and a minimum follow-up of 24 months.

## Methods

The study was approved by the institutional review boards or ethics committees of all participating centers, and all patients provided written informed consent before entering the study. The trial protocol and statistical analysis plan are included in [Supplement 1](#).

## Study Population

Patients eligible for this study were aged 18 years or older, had a Karnofsky performance score of 70 or higher (a score of  $\geq 70$  ensures independence in activities of daily living), and had newly diagnosed and histologically confirmed supratentorial glioblastoma (World Health Organization [WHO] grade IV astrocytoma<sup>15</sup>). All participants had undergone maximal safe debulking surgery when feasible or biopsy and had completed standard radiotherapy with concomitant temozolomide at the time of enrollment. Prior use of implanted

## Key Points

**Question** Does the use of tumor-treating fields (TTFields), consisting of low-intensity, alternating electric fields delivered via transducer arrays applied to the scalp, when added to maintenance temozolomide chemotherapy, improve progression-free survival for patients with glioblastoma?

**Findings** In this randomized clinical trial involving 695 patients with glioblastoma who had completed initial radiochemotherapy, median progression-free survival from randomization was 6.7 months in the TTFields plus temozolomide group and 4.0 months in the temozolomide-alone group (hazard ratio, 0.63), a significant difference.

**Meaning** Among patients with glioblastoma, the addition of TTFields to maintenance temozolomide chemotherapy resulted in statistically significant improvement in survival. These results are consistent with those reported in a previous interim analysis.

carmustine wafers was allowed. Patients with evidence of progressive disease following radiochemotherapy, infratentorial tumor location, and severe comorbidities were excluded. Adequate hematological, liver, and kidney function tests to allow for temozolomide chemotherapy were required.<sup>6,14,16</sup>

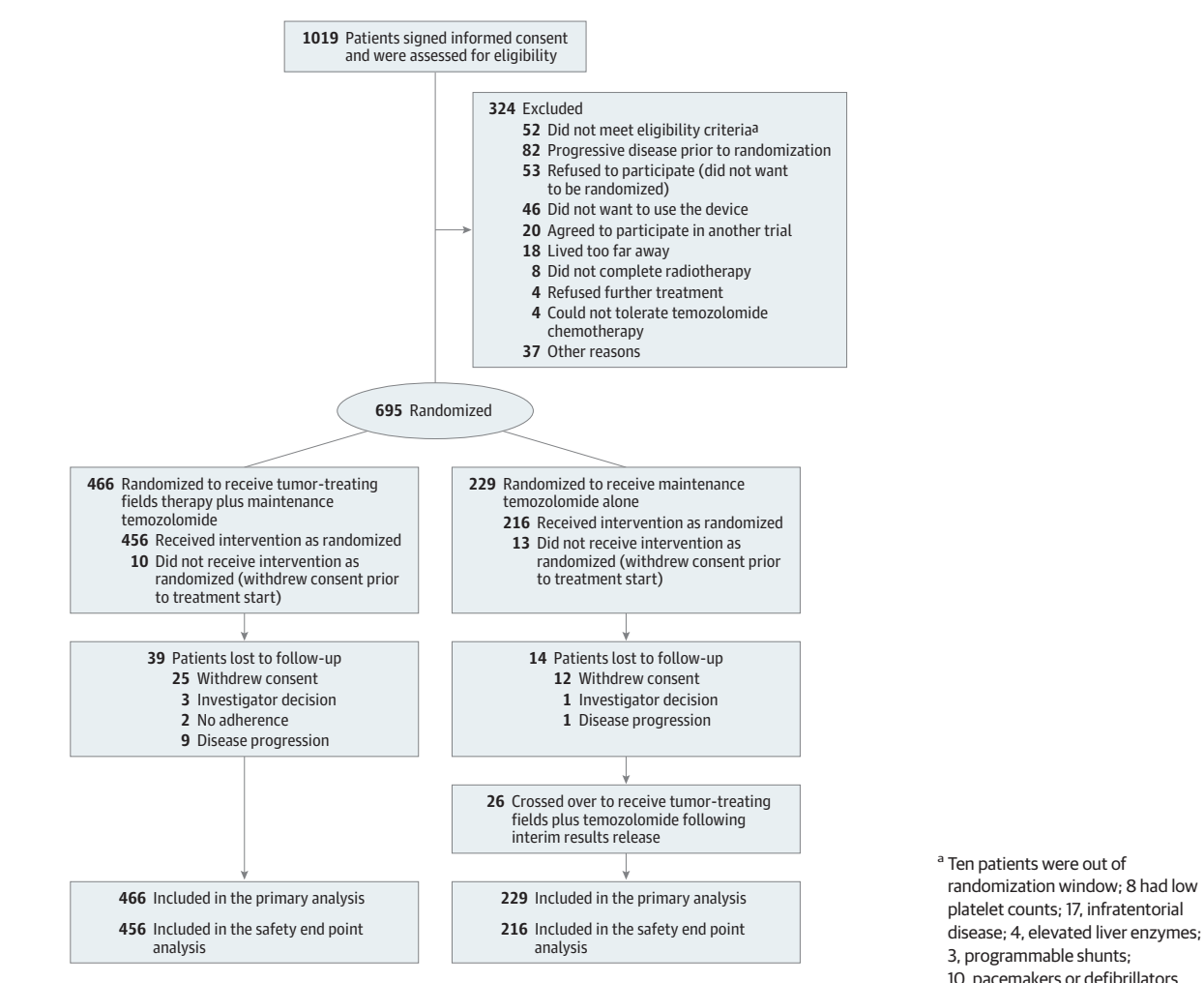
## Study Design and Treatment

This multicenter, open-label, randomized clinical phase 3 trial, recruited 695 patients at 83 sites in North America, Europe, the Republic of Korea, and Israel. The trial was designed to test the efficacy and safety of TTFields in combination with best standard of care in the treatment of newly diagnosed glioblastoma. Patients were randomized after the end of radiochemotherapy at a ratio of 2:1 to receive standard maintenance temozolomide chemotherapy (150-200 mg/m<sup>2</sup>/d for 5 days every 28 days for 6 cycles) with or without the addition of TTFields. Tumor treating fields treatment was to be initiated at least 4 weeks but not more than 7 weeks from the last day of radiotherapy. Maintenance temozolomide was delivered in 28-day cycles according to the protocol established by the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada (NCIC) Clinical Trials Group.<sup>6</sup> Extension of the duration of maintenance temozolomide beyond 6 cycles was allowed per local practice. Randomization was performed using a central web-based randomization system and was stratified by extent of resection (biopsy, partial resection, gross total resection) and by the methylation status of the O6-methylguanine-DNA methyltransferase (*MGMT*) gene promoter (methylated, unmethylated, unknown).

Treatment with TTFields was delivered through 4 transducer arrays with 9 insulated electrodes each placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain (Optune, Novocure Inc). Transducer array layouts were determined using a TTFields mapping software system to optimize field intensity within the treated tumor (NovoTAL, Novocure Inc). Patients were trained by the nursing staff and device technician to operate the device independently, replace transducer arrays, and troubleshoot any



Figure 1. Recruitment and Inclusion of Patients in the Study



alarm conditions (eg, disconnected cables). All treatment was delivered on an outpatient basis and at home. The transducer arrays were supplied in individual sterile packages, and replaced by the patient, a caregiver, or a device technician twice a week. Although uninterrupted treatment was recommended, the patient could take short treatment breaks to tend to personal needs. The patient was advised to continue treatment for no fewer than 18 hours a day.

If tumor progression occurred, second-line therapy was offered per local practice. However, in the experimental group, TTFields could be continued until second radiologic progression occurred or for a maximum of 24 months.

### Patient Surveillance and Follow-up

Patients diagnosed with glioblastoma who had undergone surgical resection or biopsy and had received standard radiochemotherapy were randomized to receive either TTFields plus temozolomide or temozolomide alone between July 2009 and December 2014 (Figure 1). The database was locked for final analysis on December 28, 2016. Baseline contrast-enhanced magnetic resonance imaging (MRI) of the brain was required within 2 weeks before starting treatment with maintenance

temozolomide with or without TTFields. A complete physical examination and laboratory parameters were performed within 1 week of treatment start. Evaluation also included the EORTC QLQ-C30 quality-of-life questionnaire with its brain-specific module (BN-20)<sup>17,18</sup> and a Mini-Mental State Examination (a test result of 27-30 points is considered normal function). Patients were seen monthly for medical follow-up and routine laboratory examinations. Quality of life was assessed every 3 months.

Adverse events were recorded for 2 months after treatment discontinuation according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) v3.0. Adverse events were presented descriptively as number and percentage of patients with each adverse event term for all patients available at the time of the analysis.

### Independent Radiological Review

Magnetic resonance imaging was performed at 2-month intervals until second progression. In the event of clinical progression, MRI was to be performed within 1 week after the investigator had become aware of it. All MRIs were reviewed by 2 blinded central independent radiologists (BioClinica Inc) and were evaluated for tumor response and progression (Macdonald criteria<sup>19</sup>). For cases



in which the 2 reviewers were not in agreement, a third blinded radiologist adjudicated between them.

### Central MGMT Testing, Pathology Review, and Molecular Analyses

In patients with paraffin-embedded tumor tissue available, evaluation of the *MGMT* methylation status was performed using quantitative methylation-specific polymerase chain reaction<sup>3,20</sup> by a central laboratory licensed by MDxHealth. If the *MGMT* methylation status could not be determined centrally prior to randomization, local *MGMT* methylation status was used for stratification. All data analyses were based on the central blinded assessment.

Patients were included based on initial local histological diagnosis. A retrospective pathology review and evaluation of molecular testing was performed by a neuropathologist (B.L.) and molecular biologist (M.E.H.). Deletion of chromosomal arms 1p and 19q and amplification of the epidermal growth factor receptor (*EGFR*) were evaluated by fluorescent in situ hybridization (FISH), immunohistochemistry (IHC), or both; and the mutation status of the isocitrate dehydrogenase 1 (*IDH1*) gene was determined by immunohistochemistry for the most common mutant *IDH1-R132H* as described previously.<sup>21</sup> For cases in which insufficient tissue was available for *EGFR* FISH, the result of *EGFR* IHC was used as a surrogate (Hirsch score,  $\geq 200$  amplified;  $< 200$ , not amplified).<sup>22</sup>

## Outcomes

### Primary and Secondary End Points

The primary end point was progression-free survival, and the secondary end point was overall survival, with analyses conducted in the intent-to-treat population.

The protocol defined that overall survival would be analyzed in a per-protocol population including only patients who received their original allocated treatments. However, 26 patients (11%) in the temozolomide-alone control group crossed over and received TTFields after December 2014, following release of the results of the interim analysis of the trial. These 26 patients had more favorable baseline characteristics than the rest of the control patients (*MGMT* methylated, 48%; Karnofsky performance score, 80-100; time from end of radiotherapy to randomization, 31 days) and received more cycles of temozolomide (median, 10.5 cycles). To avoid possible bias, these patients were analyzed as randomized in the control group according to the intent-to-treat principle.

### Exploratory End Points

Other predefined exploratory end points were percentage of patients alive and progression free at 6 months, annualized survival rates, quality of life, Mini-Mental State Examination, and Karnofsky performance score. The quality-of-life data are not reported in this article.

## Statistical Analysis

### Primary and Secondary End Points

For the primary end point of progression-free survival, the calculated sample size was 700 patients aimed to detect a hazard ratio (HR) of 0.78 or less, with 80% power allowing for 10%

loss to follow-up and a 2-sided  $\alpha = .05$ . Overall survival was a powered secondary end point in the study (80% power; HR, 0.76; 2-sided  $\alpha = .05$ ). To avoid multiplicity, overall survival was to be tested statistically only if the primary end point of the study was met.

To allow for 2 analyses in the trial, the final type I error of 0.05 was split between the interim and final analyses based on a standard  $\alpha$  spending function (Lan and DeMets<sup>23,24</sup>). The primary end point at the final analysis would be achieved if progression-free survival was significantly longer in the TTFields plus temozolomide group using a stratified log-rank test (stratified by the randomization strata) with an  $\alpha$  of .046 (an  $\alpha$  of 0.014 was spent on the interim analysis).

The secondary end point would be achieved at the final analysis if overall survival was significantly longer in the TTFields plus temozolomide group using a stratified log-rank test with an  $\alpha$  of .048 (an  $\alpha$  of .006 was spent on the interim analysis).

### Missing Data

For the analysis of progression-free survival patients were censored for progression when treatment was changed before evidence of progression (at the date of treatment change), at the date of their last MRI if lost to follow up, or upon reaching the cutoff date without progression. For the analysis of overall survival, patients without a known date of death were censored at the last known date they were documented to be alive.

### Exploratory End Points

The exploratory end points of annual survival rates and the rate of progression-free survival at 6 months were compared between groups using a 1-sided *Z* distribution of the Kaplan-Meier estimates of the survival rates at the defined time point. In addition, the Cox proportional hazards model was used to analyze both progression-free survival and overall survival controlling for treatment group, age, sex, *MGMT* methylation status (as determined by the central laboratory), tumor location in the brain, and country of residence (United States vs all other countries). The threshold for significant interactions in the model was specified at an  $\alpha$  of .05.

### Post Hoc Analysis

Post hoc analyses of prespecified subgroups (*MGMT* promoter methylation status, extent of resection (complete, partial resection, or biopsy), age (continuous), performance status (90-100 vs  $\leq 80$ ), sex, and geographic region (United States vs the rest of the world) was performed using a multivariate analysis testing the difference between treatment groups while controlling for the other prognostic factors.

### Analysis of Adverse Events and Tolerability

Differences in the incidence of adverse events between groups was tested using a  $\chi^2$  test at an  $\alpha$  of .05. The incidence of adverse events was also compared between groups after normalizing the incidence to the average treatment duration per group. Differences in the time to decline in Karnofsky performance score and Mini-Mental State Examination were tested using a log-rank test at an  $\alpha$  of .05. All analyses were performed using SAS version 9.4.



Table 1. Patient and Treatment Characteristics

Characteristics	No. (%) of Patients	
	TTFields + Temozolomide (n = 466)	Temozolomide Alone (n = 229)
Age, y		
Median (range)	56.0 (19-83)	57.0 (19-80)
≥65	89 (19)	45 (20)
<65	377 (81)	184 (80)
Karnofsky performance score <sup>a</sup>		
Median (range)	90.0 (60-100)	90.0 (70-100)
90-100	308 (66)	149 (65)
≤80	154 (33)	74 (32)
Missing	4 (1)	6 (3)
Sex		
Men	316 (68)	157 (69)
Women	150 (32)	72 (31)
Region		
United States	221 (47)	118 (52)
Outside the United States	245 (53)	111 (48)
Race/ethnicity		
White	416 (89)	201 (88)
African American	3 (1)	1 (<1)
Asian	27 (6)	19 (8)
Hispanic	18 (4)	7 (3)
American Indian	1 (<1)	1 (<1)
Antiepileptic drug use at baseline	205 (44)	95 (41)
Corticosteroid use at baseline	135 (29)	64 (28)
Mini-Mental State Examination score <sup>b</sup>		
27-30	356 (76)	160 (70)
≤26	88 (19)	48 (21)
Missing	22 (5)	21 (9)
Extent of resection		
Biopsy	60 (13)	29 (13)
Partial resection	157 (34)	77 (33)
Gross total resection	249 (53)	123 (54)
MGMT promotor region methylation status		
Tissue available and tested	386 (83)	185 (81)
Methylated	137 (36)	77 (42)
Unmethylated	209 (54)	95 (51)
Invalid	40 (10)	13 (7)
Slides available for central pathology review	296 (64)	138 (60)
Confirmed glioblastoma	285 (96)	134 (97)
WHO grade II or III glioma	4 (1)	2 (1)
Insufficient quality for diagnosis	7 (2)	2 (1)
IDH1-R132H status		
Tissue available and tested	260 (56)	119 (52)
Mutated	19 (7)	6 (5)
Negative test results	240 (92)	113 (95)
Invalid	1 (<1)	
EGFR status		
Tissue available and tested	252 (54)	112 (49)
Amplified	102 (41)	43 (38)
Not amplified	147 (58)	68 (61)
Invalid	3 (1)	1 (1)
Tumor tissue chromosomes 1p and 19q		
Tissue available and tested	259 (56)	112 (49)
Codeletion	2 (1)	
Loss 1p only	4 (2)	1 (1)
Loss 19q only	3 (1)	3 (3)
Retained	239 (92)	102 (91)
Invalid	11 (4)	6 (5)

(continued)

Table 1. Patient and Treatment Characteristics (continued)

Characteristics	No. (%) of Patients	
	TTFields + Temozolomide (n = 466)	Temozolomide Alone (n = 229)
Tumor position <sup>c</sup>		
Corpus callosum	25 (5)	12 (5)
Frontal lobe	190 (41)	84 (37)
Occipital lobe	58 (12)	27 (12)
Parietal lobe	146 (31)	89 (39)
Temporal lobe	191 (41)	90 (40)
Missing	3 (1)	3 (1)
Tumor location <sup>c</sup>		
Left hemisphere	214 (46)	99 (43)
Right hemisphere	249 (53)	127 (55)
Both hemispheres	4 (1)	2 (1)
Corpus callosum	15 (3)	9 (4)
Missing	1 (<1)	1 (<1)
Treatment delivery		
Completed standard radiation therapy		
57-63 Gy	422 (91)	212 (93)
<57 Gy	21 (5)	11 (5)
>63 Gy	18 (4)	3 (1)
Dose not reported	5 (1)	3 (1)
Concomitant radiation therapy and temozolomide		
Yes	433 (93)	212 (93)
No record available	33 (7)	17 (7)
Time from last day of radiation treatment to randomization, median (range), d	37 (15-128)	36 (15-70)
Time from initial diagnosis to randomization, median (range), mo	3.8 (1.7-6.2)	3.7 (1.4-6.3)
Temozolomide cycles, median (range)	6 (0-51)	5 (0-33)
Tumor-treating fields therapy		
Duration, median (range), mo	8.2 (0-82)	
≥18 h/d (first 3 mo of treatment), mean	347 (75)	

Abbreviations: *EGFR*, epidermal growth factor receptor gene; *IDH1*-R132H, isocitrate dehydrogenase 1 (*IDH1*) R132H mutation site; *MGMT*, O<sup>6</sup>-methylguanine-DNA-methyltransferase gene; TTFields, tumor-treating fields; WHO, World Health Organization.

<sup>a</sup> Karnofsky performance score ranges from 0 to 100 in 10-point increments, with a higher score representing better performance status.

<sup>b</sup> Scores range from 1 to 30, with a higher score representing better cognitive function.

<sup>c</sup> Multiple positions for each patient allowed (for multifocal tumors).

## Results

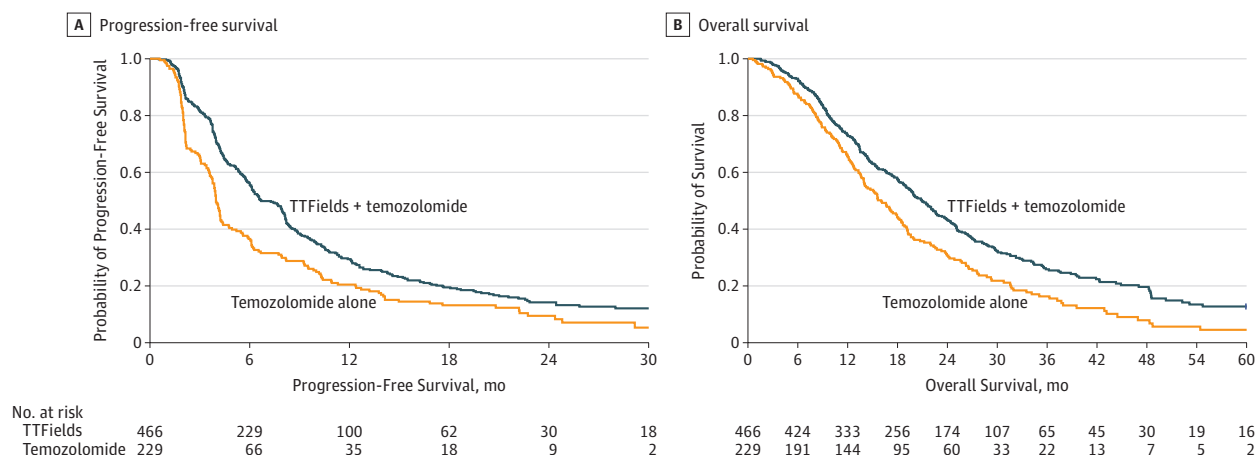
### Study Participants

Four hundred and sixty-six patients were randomized to receive TTFields plus temozolomide and 229 to receive temozolomide alone (Figure 1). Patient baseline characteristics were balanced between the 2 groups (Table 1). The median age was 56 years (interquartile range [IQR], 48-63 years), 68% were men, and median Karnofsky performance score was 90%. Eighty-nine percent of patients were white, and 49% of the patients were treated in the United States.

Fifty-four percent had undergone a gross total resection (>95% of the tumor removed; as assessed and reported by the surgeon), 13% of patients had a diagnostic biopsy only. Histological slides for central pathology review were available for



Figure 2. Kaplan-Meier Survival Curves for Patients Included in the Final Analysis in the Intent-to-Treat Population



A, Median progression-free survival from randomization for the tumor-treating fields (TTFields) plus temozolomide group was 6.7 months and was 4.0 months for the temozolomide-alone group (hazard ratio [HR], 0.63; 95% CI, 0.52-0.76;  $P < .001$ ). B, Median survival from randomization was 20.9 months for the TTFields plus temozolomide group vs 16.0 months for the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76;  $P < .001$ ). Median follow-up was 44 months (range, 25-91 months) in both groups.

434 of 695 patients (62%). The local diagnosis of glioblastoma was confirmed in 419 of 434 patients (97%). For 6 cases WHO grade II or III diagnoses were made, and for the remaining 9 patients, the available tissue for review did not allow for a definitive diagnosis or showed no tumor, yet all these patients were included in the intent-to-treat analysis. Tumor tissue for *MGMT* testing was available for 82% of the patients; of the cases with a valid test (518 of 571) 41% were *MGMT* methylated (40% TTFields plus temozolomide group and 45% for the temozolomide-only group). In 7% of tumors, expression of the *IDH1*-R132H mutant was demonstrated by a positive immunohistochemistry, *EGFR* was amplified in 40%.

Tumor location (lobe, hemisphere) in the brain was also comparable between the groups. The median time from histological diagnosis to randomization was 3.8 months (range, 1.7-6.2 months) for patients in the TTFields plus temozolomide group, and 3.7 months (range, 1.4-6.3 months) for those in the temozolomide-only group. Median time from the end of radiotherapy to randomization was 37 days in the TTFields plus temozolomide group and 36 days in the temozolomide-only group and occurred in most patients after starting of the first cycle of maintenance temozolomide. Median time from randomization to TTFields was 5 days (IQR, 3-7 days).

### Treatment Delivery

All patients had completed radiotherapy and concomitant temozolomide as per local practice. The median number of temozolomide cycles until first tumor progression was 6 (range, 0-51) for the TTFields plus temozolomide group and 5 (range, 0-33) for the temozolomide-only group; the median duration of TTFields treatment was 8.2 months (range, 0-82 months), 51% ( $n = 237$ ) of patients continued TTFields after the first progression.

### Efficacy End points

After a median follow-up of 40 months (IQR, 34-66 months), and a minimum follow-up of 24 months, the primary end point

of median progression-free survival was 6.7 months (95% CI, 6.1-8.1 months) for patients treated with TTFields plus temozolomide vs 4.0 months (95% CI, 3.8-4.4 months) for patients treated with temozolomide alone, for a proportional hazard ratio (HR) of 0.63 (95% CI, 0.52-0.76;  $P < .001$ ; stratified log-rank test; Figure 2A). For the secondary end point of overall survival, the median survival duration from randomization was 20.9 months (95% CI, 19.3-22.7 months) in the TTFields plus temozolomide group vs 16.0 months (95% CI, 14.0-18.4 months) in the temozolomide-only group, proportional HR of 0.63 (95% CI, 0.53-0.76;  $P < .001$ ; stratified log-rank test; Figure 2B).

In exploratory analyses, the percentage of patients alive at 2 years from randomization was 43% (95% CI, 39%-48%); at 3 years, 26% (95% CI, 22%-31%), and at 5 years, 13% (95% CI, 9%-18%) in the TTFields plus temozolomide group and for the temozolomide-only group at 2 years was 31% (95% CI, 25%-38%;  $P < .001$ ); at 3 years, 16% (95% CI, 12%-23%;  $P = .009$ ); and at 5 years, 5% (95% CI, 2%-11%;  $P = .004$ ). Progression-free survival at 6 months was 56% (95% CI, 51%-61%) for patients treated with TTFields plus temozolomide and 37% (95% CI, 30%-44%) with temozolomide only ( $P < .001$ ) (Table 2).

An exploratory Cox proportional hazards model adjusting for Karnofsky performance score, *MGMT* promoter methylation status, geographic region, age, tumor location, and extent of resection were consistent with the findings of the progression-free and overall survival analyses. The following factors were associated with longer overall survival: TTFields plus temozolomide treatment (HR, 0.63; 95% CI, 0.53-0.76;  $P < .001$ ), female sex (HR, 0.76, 95% CI, 0.63-0.92;  $P = .005$ ), methylated *MGMT* promoter (HR, 0.50; 95% CI, 0.41-0.62;  $P < .001$ ), younger age (as a continuous variable; HR, 0.978 per year; 95% CI, 0.969-0.985;  $P < .001$ ) and higher Karnofsky performance score (as a categorical variable in 10 point increments;  $P < .001$ ). Patients with frontal tumors had non-significantly longer survival (HR = 0.82, CI 0.67-1.01,  $P = .061$ ). Country of treatment and extent of resection were not



Table 2. Summary of Study End Points<sup>a</sup>

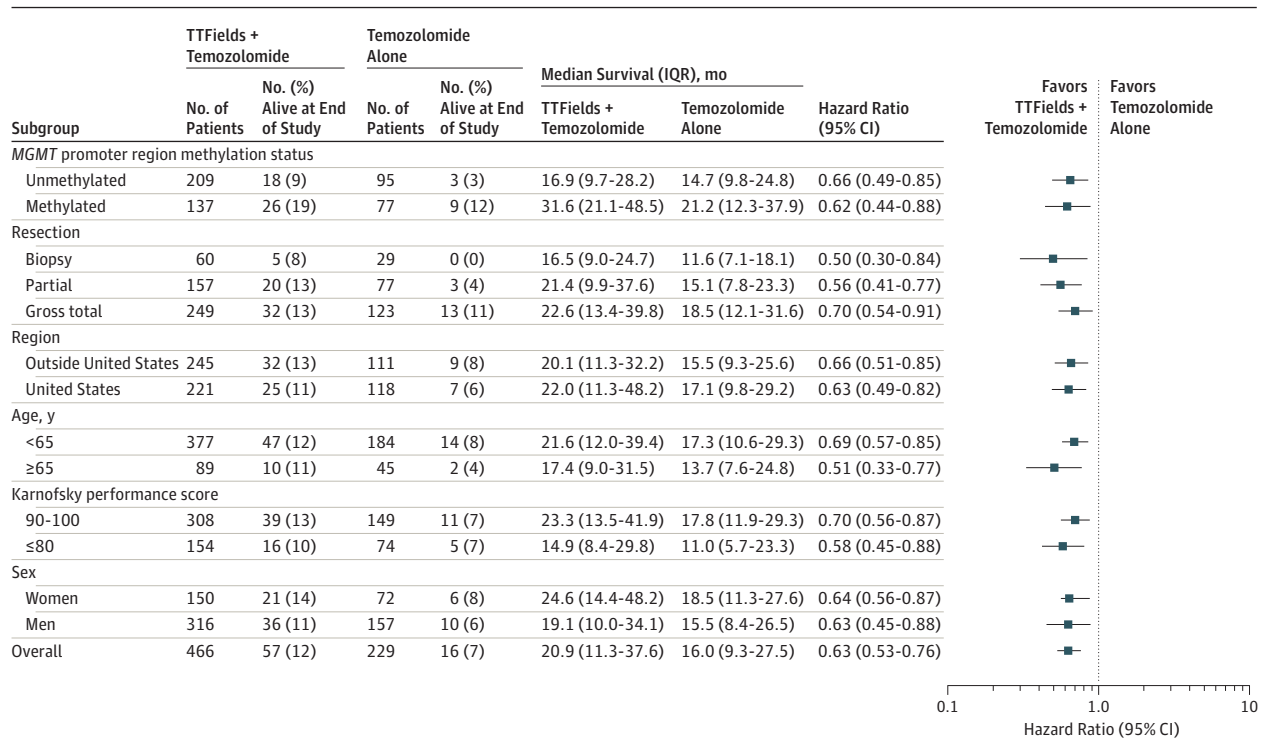
	TTFields + Temozolomide (n = 466)	Temozolomide Alone (n = 229)	Between-Group Differences
Progression-free survival			
Primary end point, median (95% CI), mo	6.7 (6.1-8.1)	4.0 (3.8-4.4)	2.7 (2.1-4.2)
Overall survival			
Secondary end point, median (95% CI), mo	20.9 (19.3-22.7)	16.0 (14.0-18.4)	4.9 (2.3-7.9)
Exploratory end points, % (95% CI)			
Progression-free 6-mo survival rate	56 (51-61)	37 (30-44)	19 (15-23)
Annual survival rates, y			
1	73 (69-77)	65 (59-72)	18 (10-25)
2	43 (39-48)	31 (25-38)	12 (4-18)
3	26 (22-31)	16 (12-23)	10 (3-17)
4	20 (16-25)	8 (4-14)	12 (5-19)
5	13 (9-18)	5 (2-11)	8 (2-14)

Abbreviation:

TTFields, tumor-treating fields.

<sup>a</sup>Survival rates are actuarial estimates according to the Kaplan-Meier method.

Figure 3. Overall Survival for Each Prognostic Patient Subgroup of Patients Treated With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone



Data points represent Cox hazard ratios of overall survival in each subgroup of patients treated with tumor-treating fields (TTFields) plus temozolomide compared with temozolomide alone and were adjusted for the other subgroups. Error bars represent 95% CIs of the hazard ratios. The Karnofsky performance score is measured from 0 to 100 in 10-point increments, with higher scores indicating better the patient performance status.

IQR, indicates interquartile range; MGMT, O<sup>6</sup>-methylguanine-DNA methyltransferase promoter region methylation status.

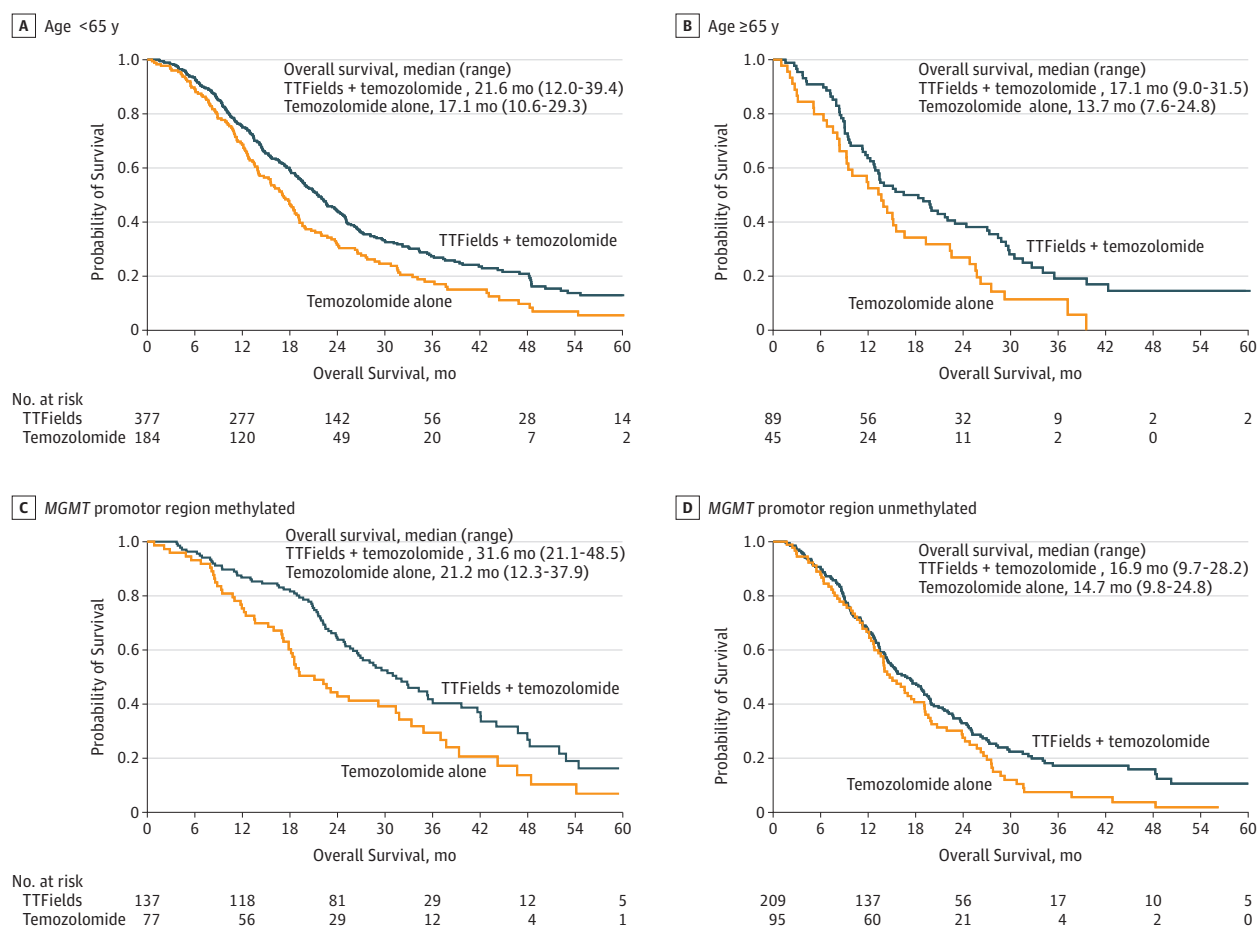
associated with a significant difference in survival ( $P = .101$  and  $P = .183$ , respectively).

### Post Hoc Subgroup Analysis

In post hoc analyses, TTFields plus temozolomide was associated with an increase in progression-free survival and overall survival (Figure 3; Cox proportional hazards,  $P < .05$  for the treatment effect within each subgroup) in all subgroups of

patients regardless of age, sex, Karnofsky performance score, MGMT promoter methylation status, geographic region, or extent of resection. Patients 65 years or older had shorter survival than patients younger than 65 years. In both age groups, TTFields plus temozolomide was associated with significantly increased survival compared with temozolomide alone for older (HR, 0.51; 95% CI, 0.33-0.77) and younger patients (HR, 0.67; 95% CI, 0.55-0.82; Figure 4A and Figure 4B).



Figure 4. Overall Survival by Patient Age and by *MGMT* Promotor Region Methylation Status

A, In comparing tumor-treating fields (TTFields) plus temozolomide vs temozolomide alone among patients younger than 65 years the hazard ratio (HR) was 0.67 (95% CI, 0.55-0.82). B, In comparing the 2 treatments among patients 65 years or older, the HR was 0.51 (95% CI, 0.22-0.77). C, In comparing the treatments among patients with O<sup>6</sup>-methylguanine-DNA methyltransferase

*MGMT* promotor region methylation, the HR was 0.62 (95% CI, 0.43-0.88). D, In comparing the treatments among patients without the *MGMT* promotor region methylation, the HR was 0.66 (95% CI, 0.49-0.85). The median follow-up of patients was 44 months (range, 25-91 months) in all groups.

Patients with tumors that lacked *MGMT* promoter methylation had a significantly shorter survival than patients with tumors with *MGMT* promoter methylation, although use of TTFields plus temozolomide was associated with longer survival (HR, 0.66; 95% CI, 0.49-0.85 both in patients with tumors that were *MGMT* methylated and tumors that were unmethylated, respectively; Figure 4C and Figure 4D). In the TTFields plus temozolomide group, 265 patients who were treated with TTFields for 18 hours a day or more (monthly average in the first 6 months of treatment) had longer survival than 185 patients treated less than 18 hours a day (22.6 months, 95% CI, 19.7-25.1 months vs 19.1 months, 95% CI, 16.5-21.9; HR, 0.65; 95% CI, 0.49-0.85;  $P = .009$ ).

### Adverse Events and Tolerability

The addition of TTFields to temozolomide therapy was not associated with any significant increase in rates of systemic adverse events compared with temozolomide therapy alone (48% vs 44%, respectively;  $P = .58$ ; Table 3), and the overall incidence,

distribution, and severity of adverse events were not statistically different in patients in the 2 treatment groups. The numerically higher incidence of some adverse events in the TTFields plus temozolomide group was a reflection of the longer duration of temozolomide treatment in this group due to delayed occurrence of progression. When adverse event incidence normalized to duration of treatment was analyzed, these differences disappeared. The only exception was a higher incidence of localized skin toxic effects (medical device site reaction beneath the transducer arrays) in patients treated with TTFields plus temozolomide; mild to moderate skin irritation was observed in 52% of patients, and severe (grade 3) skin involvement occurred in 2%. Anxiety, confusion, insomnia, and headaches which were reported more frequently (statistically nonsignificant) in patients treated with TTFields at the interim analysis were not seen in the final adverse event analysis of the trial. The incidence of seizures was identical in the 2 groups.

To estimate tolerability, prespecified exploratory analyses of the association of TTFields device use with patients'



Table 3. Adverse Events by Body System and Severity ( $\geq 5\%$  Incidence in Any Group)

	Grade 3-4 Events, No. (%) of Patients	
	TTFields + Temozolomide (n = 456)	Temozolomide Alone (n = 229)
$\geq 1$ Adverse event	218 (48)	94 (44)
Blood and lymphatic system disorders <sup>a</sup>	59 (13)	23 (11)
Thrombocytopenia	39 (9)	11 (5)
Gastrointestinal disorders	23 (5)	8 (4)
Asthenia, fatigue, and gait disturbance	42 (9)	13 (6)
Infections	32 (7)	10 (5)
Injury, poisoning, and procedural complications (falls and medical device site reaction)	24 (5)	7 (3)
Metabolism and nutrition disorders (anorexia, dehydration, and hyperglycemia)	16 (4)	10 (5)
Musculoskeletal and connective tissue disorders	21 (5)	9 (4)
Nervous system disorders	109 (24)	43 (20)
Seizures	26 (6)	13 (6)
Respiratory, thoracic and mediastinal disorders (pulmonary embolism, dyspnea, and aspiration pneumonia)	24 (5)	11 (5)

Abbreviation:

TTFields, tumor-treating fields.

<sup>a</sup> The numerically slightly higher incidence of hematological toxicity, fatigue, and some other adverse effects are due to the longer treatment duration and observation time in the experimental group. The differences disappear when data are normalized to treatment duration.

activities of daily life and cognition were performed using the Karnofsky performance score and the Mini-Mental State Examination. Time to a sustained 6-point decline in the Mini-Mental State Examination score was significantly longer in the TTFields plus temozolomide group than the temozolomide-alone group (16.7 months, 95% CI, 14.7-19.0 months vs 14.2 months, 95% CI, 12.7-17.0 months, respectively; HR, 0.79; 95% CI, 0.66-0.95;  $P = .01$ ). Time to a sustained 10-point decrease in Karnofsky performance score was also significantly longer in the TTFields plus temozolomide group than in the temozolomide-alone group (5.5 months, 95% CI, 5.0-6.3 months vs 3.9 months, 95% CI, 3.1-5.2 months, respectively; HR, 0.80; 95% CI, 0.67-0.95;  $P = .009$ ).

## Discussion

In the final analysis of this randomized phase 3 trial, the addition of the TTFields treatment to standard temozolomide maintenance therapy, compared with standard temozolomide maintenance therapy alone, resulted in increased progression-free survival and overall survival in patients with newly diagnosed glioblastoma. After a median follow-up of 40 months, the addition of TTFields to temozolomide, compared with temozolomide alone, resulted in longer median progression-free survival from the time of randomization, 6.7 months vs 4.0 months and longer median overall survival from randomization, 20.9 months vs 16.0 months, respectively. These findings are consistent with the preliminary results reported based on a planned interim analysis of the first 315 patients enrolled, after a median follow-up of 38 months, in which median progression-free survival in the intent-to-treat population was 7.1 months (95% CI, 5.9-8.2 months) in the TTFields plus temozolomide group (210 patients analyzed) and 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide-alone group (105 patients analyzed).

In the current study, exploratory end points were consistent with the primary and secondary end points in this trial. In a post hoc analysis the effect of TTFields was observed in all clinical and molecular subgroups, including patients older than age 65 years and patients with *MGMT* unmethylated tumors.

To assess whether the improved outcome may have been related to other factors than the TTFields therapy the data were scrutinized for possible imbalances, unexpected poor performance of the control group, or differences in supportive care administered to patients between the 2 groups. Both clinical factors and molecular tumor characteristics were well balanced and comparable between the 2 groups. *MGMT* promoter methylation, the strongest predictive factor for outcome in temozolomide-treated patients,<sup>25</sup> was more prevalent in the control group (45% vs 40% of samples with a valid result). Patients with early tumor progression occurring during the first 3 months after diagnosis were not included in this trial, and so the randomized patient population had a better prognosis, for both groups, compared with other trials that had randomized patients before radiation therapy. The reported survival times were measured from randomization, not from diagnosis, so for an estimation of the overall outcome 3.8 months should be added in both groups. The RTOG 0525/Intergroup study, which evaluated dose-dense temozolomide, also randomized patients only after completion of radiochemotherapy.<sup>8</sup> Outcome of the control group in the current study and of the RTOG study were very similar, and in both studies, the median survival from randomization was 16 months.

In this trial, the rates of systemic adverse effects were not significantly different in the 2 treatment groups. The occurrence of mild to moderate skin irritation related to reaction beneath the transducer arrays of the device occurred in more than half of patients in the TTFields plus temozolomide group.

These findings are in contrast to the more than 23 randomized trials conducted over the last decade that have evaluated novel agents or intensified treatment strategies



(eg, dose-dense temozolomide, cilengitide, nimotuzumab, bevacizumab, and rindopepimut<sup>3,5,8,26</sup>) for treatment of patients with newly diagnosed glioblastoma and have failed to demonstrate improved survival. Innovative treatments for glioblastoma are needed.

### Limitations

This study has several limitations. First, the current trial was open-label because it was considered practically unfeasible (heat and easy measure of current associated with TTFields) and ethically unacceptable to expose patients to a sham device. Although a placebo effect may affect subjective end points like quality of life or even progression-free survival by influencing the frequency of imaging and its interpretation, in the current trial a consistent benefit was observed in progression-free survival as assessed by blinded central radiology review, as well as in the gold standard of objective outcome, overall survival. Second, delivery of TTFields therapy requires the patient to continuously carry a device on a

shaved scalp and may create burdens for patients. Nevertheless, the majority of patients were able to handle the device independently or with some help from a caregiver. The fact that 75% of patients achieved treatment adherence of 75% or more (ie, using the device for  $\geq 18$  hours per day) indicated good tolerability. The effects of the TTFields treatment and the need for continuous use of the device on quality of life will be reported separately.

### Conclusions

In the final analysis of this randomized clinical trial of patients with glioblastoma who had received standard radiochemotherapy, the addition of TTFields to maintenance temozolomide chemotherapy vs maintenance temozolomide alone, resulted in statistically significant improvement in progression-free survival and overall survival. These results are consistent with the previous interim analysis.

### ARTICLE INFORMATION

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# Influence of Treatment With Tumor-Treating Fields on Health-Related Quality of Life of Patients With Newly Diagnosed Glioblastoma

## A Secondary Analysis of a Randomized Clinical Trial

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**IMPORTANCE** Tumor-treating fields (TTFields) therapy improves both progression-free and overall survival in patients with glioblastoma. There is a need to assess the influence of TTFields on patients' health-related quality of life (HRQoL).

**OBJECTIVE** To examine the association of TTFields therapy with progression-free survival and HRQoL among patients with glioblastoma.

**DESIGN, SETTING, AND PARTICIPANTS** This secondary analysis of EF-14, a phase 3 randomized clinical trial, compares TTFields and temozolomide or temozolomide alone in 695 patients with glioblastoma after completion of radiochemotherapy. Patients with glioblastoma were randomized 2:1 to combined treatment with TTFields and temozolomide or temozolomide alone. The study was conducted from July 2009 until November 2014, and patients were followed up through December 2016.

**INTERVENTIONS** Temozolomide, 150 to 200 mg/m<sup>2</sup>/d, was given for 5 days during each 28-day cycle. TTFields were delivered continuously via 4 transducer arrays placed on the shaved scalp of patients and were connected to a portable medical device.

**MAIN OUTCOMES AND MEASURES** Primary study end point was progression-free survival; HRQoL was a predefined secondary end point, measured with questionnaires at baseline and every 3 months thereafter. Mean changes from baseline scores were evaluated, as well as scores over time. Deterioration-free survival and time to deterioration were assessed for each of 9 preselected scales and items.

**RESULTS** Of the 695 patients in the study, 639 (91.9%) completed the baseline HRQoL questionnaire. Of these patients, 437 (68.4%) were men; mean (SD) age, 54.8 (11.5) years. Health-related quality of life did not differ significantly between treatment arms except for itchy skin. Deterioration-free survival was significantly longer with TTFields for global health (4.8 vs 3.3 months;  $P < .01$ ); physical (5.1 vs 3.7 months;  $P < .01$ ) and emotional functioning (5.3 vs 3.9 months;  $P < .01$ ); pain (5.6 vs 3.6 months;  $P < .01$ ); and leg weakness (5.6 vs 3.9 months;  $P < .01$ ), likely related to improved progression-free survival. Time to deterioration, reflecting the influence of treatment, did not differ significantly except for itchy skin (TTFields worse; 8.2 vs 14.4 months;  $P < .001$ ) and pain (TTFields improved; 13.4 vs 12.1 months;  $P < .01$ ). Role, social, and physical functioning were not affected by TTFields.

**CONCLUSIONS AND RELEVANCE** The addition of TTFields to standard treatment with temozolomide for patients with glioblastoma results in improved survival without a negative influence on HRQoL except for more itchy skin, an expected consequence from the transducer arrays.

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 Invited Commentary

 Supplemental content

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Glioblastoma has a poor prognosis,<sup>1,2</sup> and, as tumors grow, patients often experience a progressive decline in neurologic function and health-related quality of life (HRQoL).<sup>3-7</sup> The current standard of care is not curative but results in prolongation of life. However, extension of survival is meaningful only if patients' functioning and well-being can be retained or improved.<sup>8-11</sup> Therefore, it is important to determine the net clinical benefit of each new treatment or treatment modality introduced; possible benefits of a new treatment, in terms of prolonged survival, have to be carefully weighed against potential negative effects of the treatment on the patients' quality of life.

The current standard of care for patients with newly diagnosed glioblastoma comprises surgical resection to the extent safely feasible followed by radiotherapy with concomitant and maintenance chemotherapy with temozolomide.<sup>12</sup> Tumor-treating fields (TTFields) (Optune; Novocure Ltd) is an antimitotic physical treatment modality<sup>13,14</sup> delivered by a home use medical device with wired transducer arrays placed on the patients' scalp. When added to standard maintenance temozolomide chemotherapy, TTFields has been demonstrated to improve both progression-free survival and overall survival in a randomized clinical trial (NCT00916409).<sup>15</sup>

Treatment with TTFields involves the patient carrying a mobile electrical device for more than 18 hours per day and having 4 arrays of transducers continuously fixed to the shaved scalp. Concerns regarding the influence of wearing the device on patients' HRQoL have therefore been raised.<sup>16,17</sup> The incidence of adverse events was not increased by the addition of TTFields to temozolomide therapy except for an expected mild to moderate skin irritation beneath the electrodes in 52% of patients (severe in 2%). Herein, we report on the influence of treatment with TTFields on the patients' HRQoL, which was a predefined secondary objective of the randomized clinical trial. The present study was conducted from July 2009 until November 2014, and patients were followed up through December 2016.

## Methods

### Study Population

Patients eligible for this study were aged 18 years or older, had newly diagnosed and histologically confirmed supratentorial glioblastoma (World Health Organization grade IV astrocytoma), were progression free after undergoing maximal safe debulking surgery or biopsy, and had completed standard radiotherapy with concomitant temozolomide. Patients were required to have a Karnofsky Performance Status score of at least 70 at the time of enrollment, corresponding to at least being able to perform self-care. Further details on the study population are available elsewhere.<sup>15</sup> All patients provided written informed consent, and the study was approved by the institutional review boards or ethics committees of all participating centers and the relevant competent authorities (eAppendix 1 in Supplement 1); the participants did not receive financial compensation.

### Key Points

**Question** What is the influence of adding tumor-treating fields to the standard treatment on health-related quality of life in patients with glioblastoma?

**Findings** In this secondary analysis of the EF-14 randomized clinical trial, the addition of tumor-treating fields did not negatively influence health-related quality of life except for itchy skin, an expected consequence from the transducer arrays.

**Meaning** Tumor-treating field therapy has previously been shown to prolong both progression-free and overall survival. When considering the net clinical benefit, improved survival without a negative influence on health-related quality of life supports the addition of tumor-treating fields to standard treatment in patients with glioblastoma.

### Study Design and Treatment

This prospective, multicenter, open-label, randomized clinical phase 3 trial recruited 695 patients at 90 medical centers in North America, Europe, the Republic of Korea, and Israel. The trial protocol is available in Supplement 2. The trial was designed to test the efficacy of TTFields in combination with the best standard of care in the treatment of newly diagnosed glioblastoma (ie, radiotherapy with concomitant and adjuvant temozolomide). The primary end point was progression-free survival, with overall survival as a powered secondary end point. Health-related quality of life was a secondary end point. Patients who were progression free after completion of radiochemotherapy were randomized within 4 to 7 weeks at a ratio of 2:1 to receive standard maintenance temozolomide chemotherapy (150-200 mg/m<sup>2</sup> for 5 days every 28 days for 6 cycles) with or without the addition of TTFields. If tolerated well, TTField therapy was to be continued until the second progression or up to 2 years.

Patients in the TTFields plus temozolomide group received continuous TTFields combined with maintenance temozolomide. TTFields were delivered through a portable device in an outpatient setting. Patients receiving TTFields had 4 transducer arrays with 9 insulated electrodes each placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain. Although uninterrupted treatment was recommended, the patient could take short breaks if needed; patients were advised to continue treatment for at least 18 hours a day. More details on the study design and treatment are published elsewhere.<sup>15</sup>

### HRQoL Assessment

The evaluation of HRQoL was performed using the validated European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-C30) and brain module (QLQ-BN20).<sup>18-20</sup> Questionnaires were completed on paper at baseline (prior to randomization) and subsequently every 3 months for up to 12 months. Nine scales and items were preselected as important based on relevance for patients with glioblastoma and hypothesized effects of the TTFields delivery device on patients' HRQoL: global health status; physical, cognitive, role, social, and emotional functioning; itchy skin;



pain; and weakness of legs. We hypothesized that any burden of carrying the device (on physical functioning and itchy skin) or detriment to social and role functioning due to the visibility of the therapy may be balanced by patients' feeling of well-being (global health status and emotional functioning) related to active participation of both the patient and the caregiver in the fight against cancer and increasing patient empowerment. Moreover, we hypothesized that treatment with TTFields would not have an influence on cognitive functioning, pain, and weakness of legs.

### Statistical Analysis

#### Calculation of HRQoL Scores

The items on both questionnaires were scaled and scored using the recommended EORTC procedures.<sup>21</sup> Raw scores were transformed to a linear scale ranging from 0 to 100, with a higher score representing a higher level of functioning or higher level of symptoms. The results of this study are presented in accordance with guidelines for reporting HRQoL in cancer clinical trials and methods.<sup>22-24</sup> Differences of at least 10 points (on a 0-100 scale) were classified as the minimum clinically meaningful change in any HRQoL scale/item.<sup>24</sup>

#### Descriptive Statistics

Descriptive statistics were used to report HRQoL scores as well as the sociodemographic and clinical variables for the population of patients who completed at least 1 HRQoL scale at baseline separately for both treatment groups. Means and SDs or medians and ranges were calculated for continuous variables depending on the distribution of the variable. Frequencies and percentages were calculated for nominal variables. Differences between arms were tested using a 2-sided  $\chi^2$  test or an independent 2-tailed, unpaired *t* test or Mann-Whitney test at an  $\alpha$  value of .05 for each variable.

Adherence to HRQoL assessments was calculated as the number of forms received divided by the number of forms expected at every assessment. Patients who completed the assessments at the time of progression were included in this analysis.

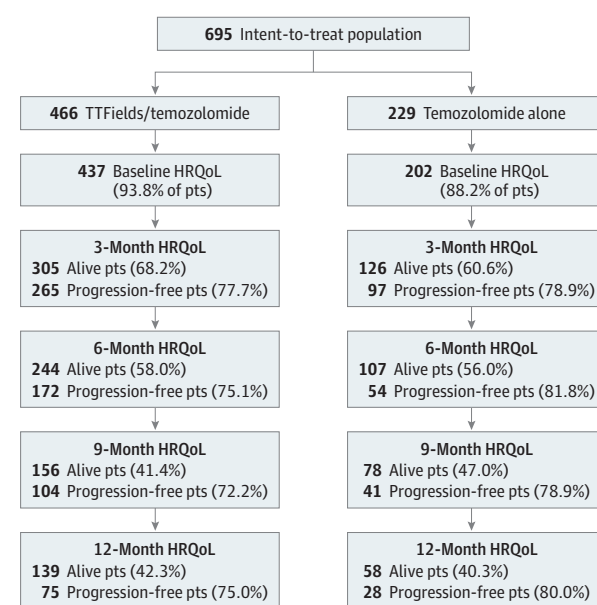
#### HRQoL Scores Over Time

Mean HRQoL scores over time were calculated as well as the mean changes from baseline. A stable HRQoL score was defined as a change of less than 10 points, and a change of 10 or more points indicated a deterioration or improvement depending on the scale or item. Mean change from baseline was plotted to evaluate the longitudinal course of patients' experience of disease and treatment, and a linear mixed-model repeated-measures analysis was used to estimate the treatment effect over time. A sensitivity analysis of complete cases using multiple imputations with a predictive mean matching regression model was used to check the robustness of the treatment effect over time. An additional sensitivity analysis used a repeated-measures model that assumes there is random variation among participants that is related to the time of dropout.

#### Stable or Improved HRQoL During the Progression-Free Period

The percentage of patients with stable (<10-point change) or improved ( $\geq$ 10-point change) HRQoL during the progression-

Figure 1. Consort Diagram



Data are the number and percentage of patients in the categories (baseline, alive, and progression-free) who completed the health-related quality-of-life (HRQoL) questionnaire at the indicated times. pts indicates patients; TTFields, tumor-treating fields.

free period, thus excluding the HRQoL assessment at progression, was determined separately for both treatment arms. This calculation was based on the total number of patients with a valid baseline HRQoL assessment and at least 1 additional follow-up assessment. Moreover, the area under the curve of stable or improved HRQoL for the entire duration of stability or improvement was determined, and differences between arms were assessed with the trapezoidal method (eAppendix 2 in Supplement 1).

#### Deterioration-Free Survival and Time to Deterioration

Deterioration-free survival was defined as the time to a greater than 10-point deterioration in scores from baseline without a subsequent 10-point or more improvement in scores compared with baseline, progressive disease, or death in the absence of a previous definitive deterioration before the next assessment. Disease progression was included as a surrogate measure. Data were censored at the last HRQoL assessment date for patients with a change of less than 10 points, patients who did not progress, or patients who died after 9 weeks since the last assessment. Data for patients with missing baseline scores were not included, and patients missing all postbaseline HRQoL assessments were censored at randomization. Time to deterioration (TTD) was defined similarly to deterioration-free survival, with the exception that progressive disease was excluded as an event (ie, nonmissing HRQoL data beyond progression were included). Kaplan-Meier methodology was used to estimate deterioration-free survival and TTD distributions and median times, and 95% CIs were computed using the Greenwood formula. The difference between treatment arms



Table 1. Baseline Demographic and Disease Characteristics

Characteristic	TTFields Plus Temozolomide (n = 437)	Temozolomide (n = 202)	All Patients (N = 639)	P Value
Age, y				
Mean (SD)	54.6 (11.4)	55.2 (11.6)	54.8 (11.5)	.50
Median (range)	56.0 (19-83)	57.0 (19-80)	56.0 (19-83)	
Sex, No. (%)				
Male	297 (68.0)	140 (69.3)	437 (68.4)	.73
Female	140 (32.0)	62 (30.7)	202 (31.6)	
Antiepileptic medication at baseline, No. (%)	174 (39.8)	79 (39.1)	253 (39.6)	.87
Corticosteroid therapy at baseline, No. (%)	129 (29.5)	60 (29.7)	189 (29.6)	.96
Region, No. (%)				
United States	203 (46.5)	97 (48.0)	300 (46.9)	.71
Canada, Europe, Israel, and Korea	234 (53.5)	105 (52.0)	339 (53.1)	
Extent of resection, No. (%)				
Biopsy	55 (12.6)	24 (11.9)	79 (12.4)	.97
Partial resection	149 (34.1)	70 (34.7)	219 (34.3)	
Gross total resection	233 (53.3)	108 (53.5)	341 (53.4)	
Tumor position, No. (%) <sup>a</sup>				
Corpus callosum	23 (5.3)	12 (5.9)	35 (5.5)	.66
Frontal lobe	177 (40.5)	74 (36.6)	251 (39.3)	
Occipital lobe	55 (12.6)	24 (11.9)	79 (12.4)	
Parietal lobe	138 (31.6)	78 (38.6)	216 (33.8)	
Temporal lobe	179 (41.0)	81 (40.1)	260 (40.7)	
Missing	2 (<1)	2 (1.0)	4 (0.6)	
Tumor location, No. (%) <sup>a</sup>				
Left	202 (46.2)	84 (41.6)	286 (44.8)	.65
Right	234 (53.5)	116 (57.4)	350 (54.8)	
Both	4 (0.9)	2 (1.0)	6 (0.9)	
Corpus callosum	14 (3.2)	9 (4.5)	23 (3.6)	
Completed radiotherapy, No. (%)				
<57 Gy	20 (4.6)	10 (5.0)	30 (4.7)	.38
60 Gy (standard; ±5%)	399 (91.3)	188 (93.1)	587 (91.9)	
>63 Gy	15 (3.4)	3 (1.5)	18 (2.8)	
Missing	3 (0.7)	1 (0.5)	4 (0.6)	
Karnofsky performance score				
Median (range)	90 (60-100)	90 (70-100)	90 (60-100)	.26
Baseline Mini-Mental State Examination score available, No. (%)				
≤26	81 (18.9)	43 (22.2)	124 (19.9)	.34
27-30	348 (81.1)	151 (77.8)	499 (80.1)	
Cycles (months) of treatment with TTFields		NA	NA	NA
No.	425			
Mean (SD)	12.5 (11.8)			
Median (range)	8.3 (0-82)			
Cycles of treatment with temozolomide				
No.	430	192	622	.02
Mean (SD)	8.9 (8.3)	7.5 (6.2)	8.5 (7.8)	
Median (range)	6.2 (0-51)	5.5 (0-33)	5.9 (0-51)	
Adherence to TTFields therapy <sup>b</sup>	327 (74.8)	NA	NA	NA

Abbreviations: Gy, gray; NA, not applicable; TTFields, tumor-treating fields.

<sup>a</sup> Multiple locations possible.

<sup>b</sup> Defined as use of the device 75% or more of the time during the first 3 months of treatment.

was compared using a 2-sided stratified log-rank test. Hazard ratios were estimated using a stratified (for extent of resection and *MGMT* status) Cox proportional hazards regression model.

SAS, version 9.4 (SAS Institute) was used for all statistical analyses, and comparisons between groups were based on the intent-to-treat principle. *P* values <.05 were considered to be



Figure 2. Changes in Global Health Status and Itchy Skin



Mean changes in points on health-related quality of life scales from baseline in global health status (A) and itchy skin with (B) with tumor-treating fields (TTFields) plus temozolomide compared with temozolomide alone. No change,

between 0 and 10 points; improvement and deterioration, changes of 10 points or more. Error bars indicate SD.

statistically significant. The Hochberg procedure was used to adjust for the multiplicity of treatment comparisons in the pre-selected HRQoL scales analyses.

## Results

### Patients

A total of 695 patients were randomly assigned in a 2:1 ratio to TTFields plus temozolomide ( $n = 466$ ) or temozolomide alone ( $n = 229$ ). A total of 639 (91.9%) patients completed at least 1 HRQoL scale at baseline: 437 (93.8%) of those in the TTFields plus temozolomide arm and 202 (88.2%) patients in temozolomide-alone arm (Figure 1). The baseline demographics of the patients who provided HRQoL data were comparable to those of the intention-to-treat population<sup>15</sup> and were well balanced between treatment arms in this subpopulation (Table 1).

### HRQoL Completion Rates and Baseline Scores

Adherence to HRQoL assessments decreased from 91.9% at baseline to 65.8% (431 of 655 patients alive) at 3 months and dropped to 41.7% (197 of 473 patients alive) at 12 months of follow-up (Figure 1). Mean and median baseline HRQoL scores were comparable between arms for all preselected scales/items (eTable 1 in Supplement 1), as well as the exploratory scales and items. Reference values of HRQoL scores of a healthy general population<sup>25</sup> were available for 7 of 9 predefined scales and items (except itchy skin and weakness of legs). Patients with glioblastoma after completion of radiochemotherapy showed clinically relevant worse functioning or more symptoms compared with the general population on all scales except pain, which was similar.<sup>25</sup>

### Mean Changes in HRQoL From Baseline and the Repeated-Measures Mixed-Effect Model

Mean changes in HRQoL over time for the global health status is presented in Figure 2A and for all 9 predefined HRQoL scales

in the eFigure in Supplement 1. Throughout the 12-month assessment period, mean changes from baseline were stable (<10-point change from baseline) for all 9 predefined HRQoL scales in both treatment arms (eFigure in Supplement 1) with the exception of itchy skin (Figure 2B). For itchy skin, a clinically relevant deterioration (ie, an increase in itchy skin) compared with baseline was seen at the month 3 evaluation in the TTFields plus temozolomide arm (mean [SD] increase, 10.4 [30.1] points vs an improvement of 2.3 [24.4] points in the temozolomide arm). For differences between treatment arms, patients treated with TTFields plus temozolomide had significantly and clinically relevant worse itchy skin at 3, 6, and 9 months than patients treated with temozolomide alone, but not at 12 months (mean [SD] increase of 10.4 [30.1] in the TTFields plus temozolomide arm vs a decrease of 2.3 [24.4] in the temozolomide-alone arm,  $P = .005$ ; increase of 8.1 [31.6] in the TTFields plus temozolomide arm vs a decrease of 4.2 [31.4] in the temozolomide-alone arm,  $P = .008$ ; increase of 5.3 [28.0] in the TTFields plus temozolomide arm vs a decrease of 5.2 [29.6] in the temozolomide-alone arm,  $P = .04$ ; increase of 4.6 [32.8] in the TTFields plus temozolomide arm vs a decrease of 1.9 [36.9] in the temozolomide-alone arm,  $P = .66$ , respectively). For all other scales, there were no statistically significant or clinically relevant differences between treatment arms.

The repeated-measures mixed-effect model supported this finding, with no statistically significant difference between treatment arms in HRQoL scores over time in any predefined scale or item except for itchy skin ( $P < .001$ ), which was worse in the TTFields plus temozolomide arm (eTable 2 in Supplement 1). The sensitivity analyses showed that the results of the linear mixed model were robust.

### Stable or Improved HRQoL During Progression-Free Time

Compared with baseline, more patients in the TTFields plus temozolomide arm compared with the temozolomide-alone arm reported stable or improved scores for global health status (53.5% vs 38.0%, respectively,  $P = .001$ ), physical func-



Table 2. Stable or Improved Health-Related Quality of Life During Progression-Free Time

Characteristic	TTFields Plus Temozolomide (n = 361)	Temozolomide (n = 142)	P Value	α Value
<b>Pain</b>				
Stable/improved from baseline, No./No. (%)	205/361 (56.8)	51/142 (35.9)	<.001	.05
Median duration (95% CI), mo	6.2 (5.9 to 7.0)	6.3 (5.6 to 9.1)	.88	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 0)	0 (0 to 0)	.80	
<b>Global health status</b>				
Stable/improved from baseline, No./No. (%)	192/359 (53.5)	53/141 (37.6)	.001	.025
Median duration (95% CI), mo	6.3 (5.9 to 7.4)	7.9 (5.9 to 9.8)	.24	
Median CFB AUC until last stable/improved status (95% CI)	24.4 (11.9 to 35.0)	65.9 (13.1 to 121.3)	.13	
<b>Physical functioning</b>				
Stable/improved from baseline, No./No. (%)	195/361 (54.0)	54/142 (38.0)	.001	.017
Median duration (95% CI), mo	6.2 (5.9 to 8.2)	9.1 (5.9 to 9.8)	.21	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 18.7)	0 (0 to 30.0)	.53	
<b>Weakness of legs</b>				
Stable/improved from baseline, No./No. (%)	206/351 (58.7)	58/138 (42.0)	.001	.013
Median duration (95% CI), mo	6.3 (6.0 to 8.3)	9.1 (5.9 to 9.8)	.08	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 0)	0 (0 to 0)	.51	
<b>Cognitive functioning</b>				
Stable/improved from baseline, No./No. (%)	181/359 (50.4)	55/142 (38.7)	.02	.01
Median duration (95% CI), mo	6.0 (4.9 to 6.5)	6.2 (5.7 to 9.6)	.65	
Median CFB AUC until last stable/improved status (95% CI)	26.3 (0 to 48.6)	0 (0 to 93.3)	.37	
<b>Emotional functioning</b>				
Stable/improved from baseline, No./No. (%)	196/359 (54.6)	62/142 (43.7)	.03	.008
Median duration (95% CI), mo	6.3 (6.0 to 8.3)	7.7 (5.8 to 9.4)	.38	
Median CFB AUC until last stable/improved status (95% CI)	22.6 (5.8 to 35.0)	25.2 (0 to 54.4)	.73	
<b>Social functioning</b>				
Stable/improved from baseline, No./No. (%)	173/359 (48.2)	58/142 (40.8)	.14	.007
Median duration (95% CI), mo	6.2 (5.9 to 7.1)	6.7 (5.9 to 9.6)	.40	
Median CFB AUC until last stable/improved status (95% CI)	16.5 (0 to 47.2)	0 (0 to 54.4)	.90	
<b>Role functioning</b>				
Stable/improved from baseline, No./No. (%)	173/361 (47.9)	58/141 (41.1)	.17	.006
Median duration (95% CI), mo	5.9 (4.4 to 6.3)	7.3 (5.7 to 9.3)	.27	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 25.0)	46.7 (0 to 75.8)	.34	
<b>Itchy skin</b>				
Stable/improved from baseline, No./No. (%)	148/349 (42.4)	64/137 (46.7)	.39	.0056
Median duration (95% CI), mo	6.0 (4.7 to 6.3)	6.7 (5.6 to 9.4)	.37	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 0)	0 (−102.2 to 0)	.19	

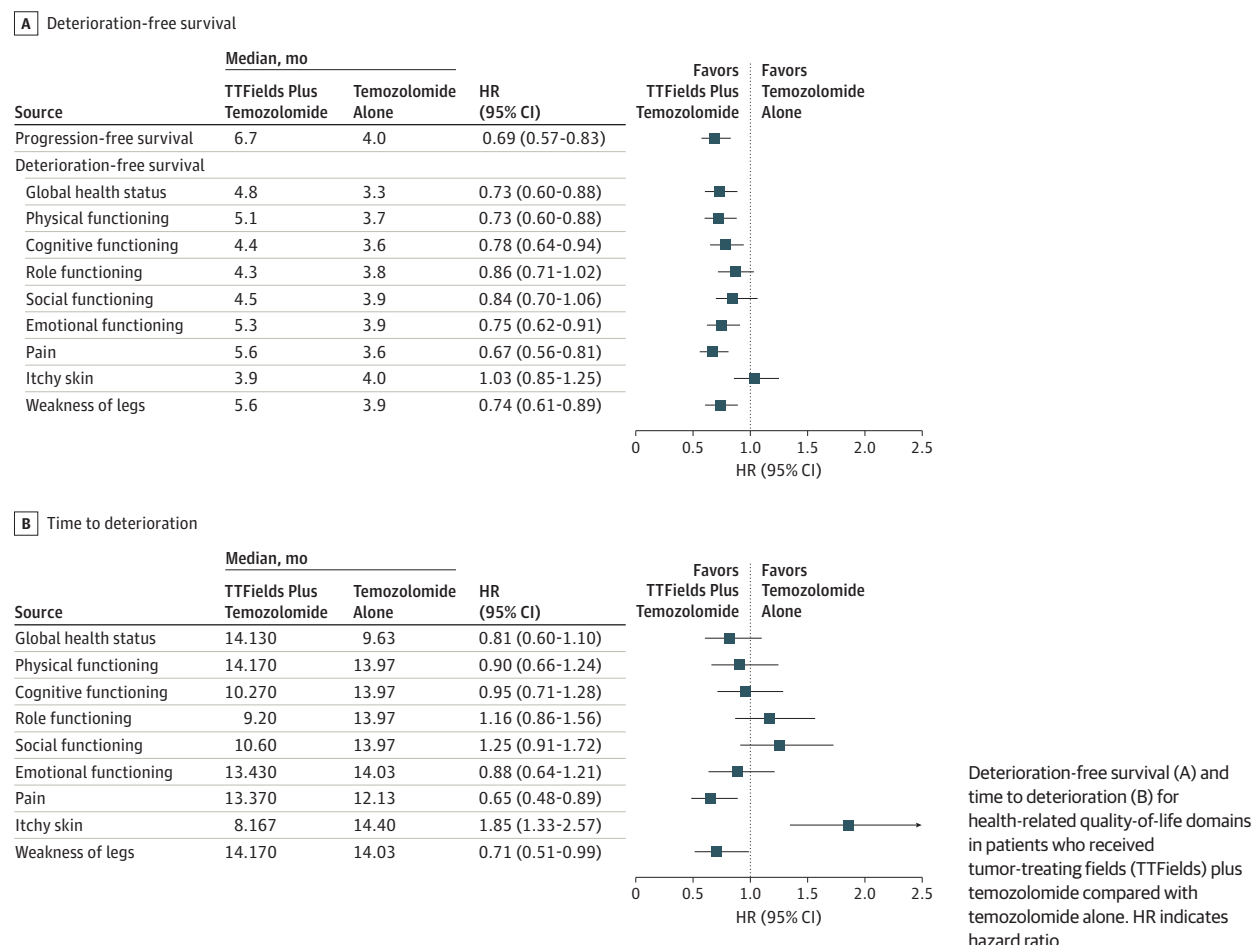
Abbreviations: AUC, area under the curve; CFB, change from baseline; TTFields, tumor-treating fields.

tioning (54.0% vs 37.0%, respectively;  $P = .001$ ), pain (56.8% vs 35.9%, respectively;  $P < .001$ ), and weakness of legs (58.7% vs 42.0%, respectively;  $P = .001$ ) but not in any of the other HRQoL scales and items. However, the duration of stable or improved HRQoL was shorter in the TTFields plus temozolomide arm, although not significantly different from the temo-

zolomide arm for any of the HRQoL scales and items. Overall, with a combination of these measures, the area under the curve analysis showed no significant differences between treatment arms for any of the HRQoL scales and items, indicating a similar HRQoL between treatment arms while patients did not experience tumor progression (Table 2).



Figure 3. Deterioration-Free Survival and Time to Deterioration



### Deterioration-Free Survival and TTD

The addition of TTFields to standard temozolomide chemotherapy resulted in statistically significant longer deterioration-free survival in global health status, physical and emotional functioning, pain, and weakness of legs (Figure 3A and eTable 2 in Supplement 1); the significant difference remained after correction for multiple testing. When progression was removed as a deterioration event (TTD), there was no negative influence of TTFields plus temozolomide treatment on the TTD of HRQoL (Figure 3B) except for itchy skin, which was worse in the TTFields plus temozolomide arm (8.2 vs 14.4 months). In contrast, the addition of TTFields to temozolomide resulted in a statistically significant prolongation until deterioration for pain (13.4 vs 12.1 months,  $P < .01$ ). There were no other significant differences in TTD between arms (Figure 3B).

### Discussion

In our detailed analysis of HRQoL during therapy with TTFields in addition to temozolomide, no significant difference was found between the groups in patients' HRQoL over time except for the skin reaction. As expected, itchy skin was reported more frequently in patients treated with TTFields be-

cause of the transducer arrays that have to be placed on the scalp of the patient. Consistently, over half of the patients also reported skin irritation as an adverse event. We had hypothesized that patients treated with TTFields may have better HRQoL in some domains as a result of active participation in the fight against cancer and the frequent interactions between patients and caregivers and device technicians regarding the device. However, on a group level, global health status and emotional functioning were not significantly different between treatment arms. Likewise, our hypotheses that the addition of TTFields would result in worse role and social functioning (due to the visibility of the device) and worse physical functioning were not confirmed. In line with our hypotheses, cognitive functioning, pain, and weakness of legs were not negatively affected by the addition of TTFields to temozolomide treatment. Most relevant for patients, HRQoL was maintained (in 8 of 9 of the predefined scales/items) over time. Combining the results of the survival and HRQoL analyses suggests that the addition of TTFields to adjuvant temozolomide is of value to patients with glioblastoma.

Patients who received TTFields had significantly longer deterioration-free survival compared with those in the temozolomide-alone arm for global health status (4.8 vs 3.3 months;  $P < .01$ ), physical (5.1 vs 3.7 months;  $P < .01$ ) and



emotional functioning (5.3 vs 3.9 months;  $P < .01$ ), pain (5.6 vs 3.6 months;  $P < .01$ ), and weakness of legs (5.6 vs 3.9 months;  $P < .01$ ). For the other scales and items, there was no significant difference in deterioration-free survival between the 2 treatment arms. The prolonged deterioration-free survival for these scales is explained by the extended progression-free survival for patients in the combined TTFields plus temozolomide arm, as progressive disease is included as an event in this analysis. Therefore, TTD analyses, excluding progressive disease as an event, is important to illustrate the influence of a treatment on HRQoL: TTD was not significantly different across any HRQoL scale or item in TTFields-treated patients except for pain and itchy skin, indicating that treatment with TTFields had an influence only on the level of pain and itchy skin. In patients treated with TTFields, TTD was significantly longer for pain (13.4 vs 12.1 months;  $P < .01$ ) and significantly shorter for itchy skin (8.2 vs 14.4 months;  $P < .001$ ). The difference between deterioration-free survival and TTD indicates the importance of disease progression (rather than treatment) as a key event driving HRQoL decline, as suggested by previous studies.<sup>26,27</sup> Moreover, in only 1% of patients, regardless of treatment arm, was a clinically relevant improvement in HRQoL seen after initial deterioration, supporting this observation. Taken together, the results of the deterioration-free survival and TTD analyses support the results of the longitudinal analysis by showing that the addition of TTFields to the standard of care did not adversely affect HRQoL. In fact, the delay in TTD for pain seen in TTFields-treated patients may reflect a delay in the occurrence of tumor-related headaches (although not significant, patients in the TTFields plus temozolomide arm had a longer TTD compared with patients in the temozolomide-alone arm for headaches: hazard ratio, 0.77; 95% CI, 0.54-1.10;  $P = .16$ ). Future studies are needed to better understand this finding, as the median TTD values for pain were longer than the median progression-free survival for both arms.

## Limitations

A common problem in many cancer clinical trials, as in this study, is missing HRQoL data. This absence is especially apparent during the follow-up period, hampering longitudinal data analysis. Patients with better prognostic factors and a good treatment response will be overrepresented at later stages.<sup>28,29</sup> However, our mixed-model analyses, accounting for missing data, confirmed the results found in the mean change from baseline analyses. Another limitation of clinical trials is generalizability of results—patients in clinical trials may not be representative of a general glioblastoma population. Patients in this trial were included only if they successfully completed the combined radiochemotherapy. In addition, it may be that not all patients are prepared to accept wearing the TTFields device. Nevertheless, patients participating in this trial were similar with respect to clinical characteristics to those participating in the EORTC 26981 study<sup>12</sup> comparing radiotherapy alone with radiotherapy plus temozolomide. Lastly, many factors may affect HRQoL, such as age, comorbidity, tumor characteristics, previous antitumor treatment (eg, radiation dose), and supportive treatment. However, it is unlikely that these factors influenced our conclusion, as the objective of this study was to compare HRQoL results between 2 treatment arms in which patients were similar due to randomization.

## Conclusions

Use of TTFields prolongs progression-free and overall survival in patients with glioblastoma. The addition of this novel device-delivered treatment neither negatively affects nor improves functioning and well-being of the patient, including critical HRQoL issues, such as role, social, and physical functioning. Patients reported more itchy skin, which is a direct and expected consequence of the placement of transducer arrays on the patients' scalp. Considering the net clinical benefit, our HRQoL data support the addition of TTFields to standard therapy in patients with glioblastoma.

## ARTICLE INFORMATION

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# Increased compliance with tumor treating fields therapy is prognostic for improved survival in the treatment of glioblastoma: a subgroup analysis of the EF-14 phase III trial

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## Abstract

**Background** Tumor treating fields (TTFields) is a non-invasive, antimitotic therapy. In the EF-14 phase 3 trial in newly diagnosed glioblastoma, TTFields plus temozolomide (TTFields/TMZ) improved progression free (PFS) and overall survival (OS) versus TMZ alone. Previous data indicate a  $\geq 75\%$  daily compliance improves outcomes. We analyzed compliance data from TTFields/TMZ patients in the EF-14 study to correlate TTFields compliance with PFS and OS and identify potential lower boundary for compliance with improved clinical outcomes.

**Methods** Compliance was assessed by usage data from the NovoTTF-100A device and calculated as percentage per month of TTFields delivery. TTFields/TMZ patients were segregated into subgroups by percent monthly compliance. A Cox proportional hazard model controlled for sex, extent of resection, *MGMT* methylation status, age, region, and performance status was used to investigate the effect of compliance on PFS and OS.

**Results** A threshold value of 50% compliance with TTFields/TMZ improved PFS (HR 0.70, 95% CI 0.47–1.05) and OS (HR 0.67, 95% CI 0.45–0.99) versus TMZ alone with improved outcome as compliance increased. At compliance  $> 90\%$ , median survival was 24.9 months (28.7 months from diagnosis) and 5-year survival rate was 29.3%. Compliance was independent of gender, extent of resection, *MGMT* methylation status, age, region and performance status (HR 0.78;  $p=0.031$ ; OS at compliance  $\geq 75\%$  vs.  $< 75\%$ ).

**Conclusion** A compliance threshold of 50% with TTFields/TMZ correlated with significantly improved OS and PFS versus TMZ alone. Patients with compliance  $> 90\%$  showed extended median and 5-year survival rates. Increased compliance with TTFields therapy is independently prognostic for improved survival in glioblastoma.

**Keywords** Glioblastoma · Tumor treating fields · Compliance · Monthly usage

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## Introduction

Glioblastoma (GBM) is the most common and aggressive adult brain tumor, accounting for 56% of all gliomas and 15% of all primary brain tumors with an annual incidence in the United States that increases with age—ranging from 0.2 per 100,000 in 0–19 year old population to the highest rate of 15.3 per 100,000 in the 75–84 year old population [1]. Glioblastoma remains incurable with a median survival of only 15 months until recently [2]. The previous standard treatments for newly diagnosed GBM include maximally safe surgical resection followed by radiation therapy (RT) and adjuvant temozolomide (TMZ) chemotherapy [3].

Tumor treating fields (TTFields) are a unique treatment modality [4, 5] for GBM that affects rapidly dividing glioma cells through the action of low-intensity, intermediate



frequency (200 kHz) alternating electric fields [6–9] that act on microtubules and septin fibers of proliferating cancer cells to disrupt mitosis, inducing mitotic cell death, mitotic catastrophe, and cellular stress characterized by autophagy, and endoplasmic reticulum stress [6–13]. TTFields inhibit DNA damage repair by the expression of DNA repair genes in the BRCA1 pathway [14] and impair cellular migration and invasion [15]. TTFields increases cell death when combined with anti-PD1, chemotherapy and radiotherapy [16–19].

The phase 3 EF-11 study of TTFields in recurrent GBM demonstrated comparable efficacy to best physician choice chemotherapy without treatment limiting systemic adverse effects [20]. Post hoc analysis of the EF-11 trial data showed significantly longer median OS with TTFields at compliance rate of  $\geq 75\%$  ( $\geq 18$  h daily) versus those with a  $< 75\%$  compliance rates [21] and high compliance rates of  $> 90\%$  with EF-11 responders [22]. The Patient Registry Dataset (PRiDe) showed significant improvement in median OS at daily compliance rates of  $\geq 75\%$  versus  $< 75\%$  [23]. The phase 3 EF-14 study in newly diagnosed GBM demonstrated that TTFields plus maintenance TMZ therapy significantly improved PFS and OS without decline in health related quality of life (HRQOL) versus TMZ alone [24–26]. The National Comprehensive Cancer Network (NCCN) has recently (2018) recommended TTFields with TMZ as a standard Category 1 treatment option for newly diagnosed GBM [27].

Unlike systemic therapies, TTFields are only active against cancer cells while the transducer arrays are placed on the scalp and the field generator is continuously administering alternating electric fields of a specific intensity (200 KHz) for GBM. There are no peak-trough fluctuations or half-life associated with TTFields. The specificity of TTFields on anti-mitotic activity of rapidly dividing glioma cells, while sparing normal cell division, enables near continuous cancer therapy with minimal systemic adverse effects. Therefore, active compliance with TTFields therapy is a critical parameter for clinical benefit.

The objective of this subgroup analysis of the EF-14 phase III trial data was to analyze compliance data to correlate TTFields compliance with PFS and OS and identify potential lower boundary for compliance rates with improved clinical outcomes.

## Methods

This subgroup analysis is based on TTFields plus TMZ and TMZ alone patient data from the EF-14 study [24]. The EF-14 trial was a randomized, open-label trial, which enrolled 695 newly diagnosed patients with GBM whose tumor was either resected or biopsied and had also

completed concomitant radiation therapy with adjuvant TMZ therapy. Patients were randomized 2:1 to TTFields plus maintenance TMZ chemotherapy ( $n=466$ ) or temozolomide alone ( $n=229$ ). Temozolomide was administered to both groups (150–200 mg/m<sup>2</sup>) for 5 days per 28-day cycle (6–12 cycles). The median time from diagnosis to randomization in both groups was 3.8 months [24].

The primary outcome of this subgroup analysis was to assess the percentage of monthly TTFields compliance as an independent predictor of PFS and OS compared with patients in the TMZ alone treatment group. Compliance data are derived from the internal computerized log file of each NovoTTF-100A (Optune®) device. Percent of the total treatment time during which the NovoTTF-100A treated patients actually received treatment was calculated by analyzing the log file of each device and dividing the total device ‘ON’ time by the prescribed number of 1 month treatment courses.

Patient compliance was calculated as the average percentage of each month the system was delivering TTFields. Progression-free survival and OS data from the TTFields plus TMZ treated group were analyzed in subgroups based on monthly compliance levels of  $< 75\%$  or  $\geq 75\%$  and finer monthly compliance bins of 0 to  $\leq 30\%$ , 30% to  $\leq 50\%$ , 50% to  $\leq 60\%$ , 60% to  $\leq 70\%$ , 70% to  $\leq 80\%$ , 80% to  $\leq 90\%$ , 90% to  $\leq 100\%$ .

The PFS and OS survival curves were constructed using the Kaplan–Meier method. Cox proportional hazards model was used to analyze treatment compliance as an independent predictor of survival controlling for treatment group, sex, *MGMT* methylation status, resection status, Karnofsky Performance Status (KPS) and country of residence (United States versus outside the United States). The threshold for significant interactions in the model was specified at an  $\alpha$  of 0.05.

## Results

In the EF-14 study, 466 patients were randomized to the TTFields plus TMZ therapy group and 229 were randomized to the TMZ alone group [24]. The patient disposition is shown in Supplementary Fig. 1. In summary, for the TTFields plus TMZ group—the majority of patients were men (68%) with a median age of 56 years, and a KPS of 90% [24]. The *MGMT* promoter region was unmethylated in 54% and methylated in 36% patients in the TTFields plus TMZ group [24]. Table 1 shows the baseline demographic characteristics of the TTFields plus TMZ group separated into subgroups based on percent compliance. Overall, the separate percent compliance groups were matched in baseline characteristics both with each other and the full data set of the primary study.



**Table 1** Baseline demographics by TTFields percent average daily compliance

% Compliance	0 to ≤30 (n=22)	30 to ≤50 (n=40)	50 to ≤60 (n=42)	60 to ≤70 (n=46)	70 to ≤80 (n=91)	80 to ≤90 (n=166)	90 to ≤100 (n=43)	TMZ alone (n=229)
Median age, years (range)	55.5 (30–70)	57.5 (25–78)	54.5 (22–79)	55.0 (20–83)	56.0 (30–78)	56.0 (28–80)	52.0 (19–68)	57.0 (19–80)
KPS, median (range)	80.0 (70–100)	90.0 (70–100)	90.0 (70–100)	90.0 (60–100)	90.0 (70–100)	90.0 (70–100)	90.0 (70–100)	90.0 (70–100)
Extent of resection, n (%)								
Biopsy only	6 (27)	4 (10)	2 (5)	8 (17)	10 (11)	23 (14)	5 (12)	29 (13)
Partial/com- plete	5 (23)	14 (35)	18 (43)	15 (33)	34 (37)	52 (31)	11 (26)	77 (34)
Gross total resection	11 (50)	22 (55)	22 (52)	23 (50)	47 (52)	91 (55)	27 (63)	123 (54)
MGMT tissue available and tested, n (%)	16 (73)	34 (85)	39 (93)	35 (76)	71 (78)	142 (86)	37 (86)	185 (81)
Methylated	5 (31.3)	14 (41.2)	12 (30.8)	13 (37.1)	24 (33.8)	49 (34.5)	15 (40.5)	77 (41.6)
Unmethyl- ated	10 (62.5)	15 (44.1)	24 (61.5)	20 (57.1)	41 (57.7)	76 (53.5)	17 (45.9)	95 (51.4)
Invalid	1 (6.3)	5 (14.7)	3 (7.7)	2 (5.7)	6 (8.5)	17 (12.0)	5 (13.5)	13 (7.0)

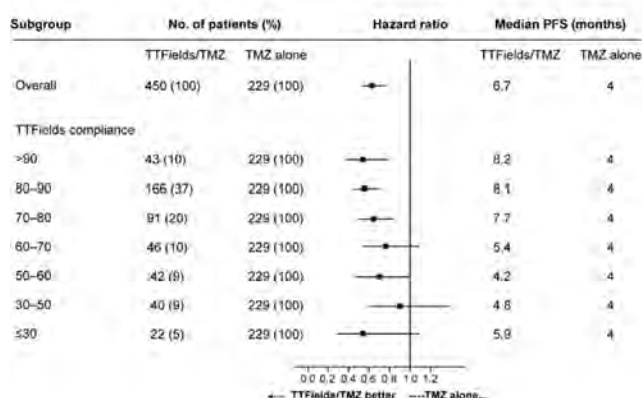
Analysis of the more refined rates of compliance (smaller bin sizes) shows a trend in favor of longer PFS and OS with progressively higher levels of monthly compliance. A threshold value of  $\geq 50\%$  average monthly compliance with TTFields plus TMZ (Fig. 1) was needed to show an extension of PFS (HR 0.70, 95% CI 0.47–1.05) and OS (HR 0.67, 95% CI 0.45–0.99) compared to TMZ alone. Both PFS and OS were extended when compliance was increased beyond 50%, indicating progressively increased gains in PFS and OS as compliance increases.

Patients with TTFields plus TMZ compliance levels of  $> 90\%$  showed maximum survival benefits (Fig. 2), with a

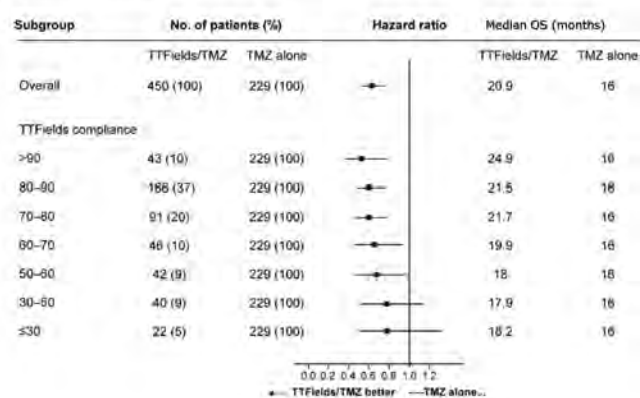
median PFS of 8.2 months for the TTFields plus TMZ group compared to 4.0 months in the TMZ alone group (HR 0.538, 95% CI 0.365–0.794;  $p=0.0047$ ) and an OS of 24.9 months (28.7 months from diagnosis since time from diagnosis to randomization was 3.8) in the TTFields plus TMZ arm compared to 16.0 months in the TMZ alone group respectively (HR 0.522, 95% CI 0.347–0.787;  $p=0.0007$ ). TTFields plus TMZ treated patients with  $> 90\%$  compliance rate had a 5-year survival rate of 29.3% (Fig. 3).

A compliance level of  $\geq 75\%$  monthly duration of treatment with TTFields plus TMZ was an independent predictor of OS, as was methylated *MGMT* status, age and KPS

### Progression-Free Survival



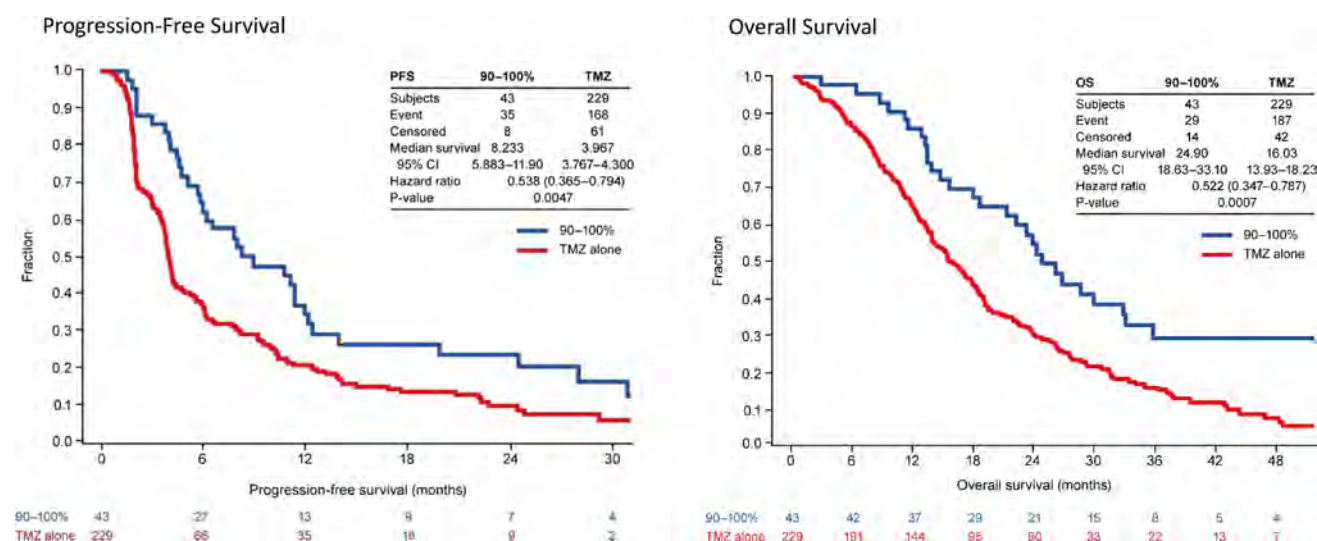
### Overall Survival



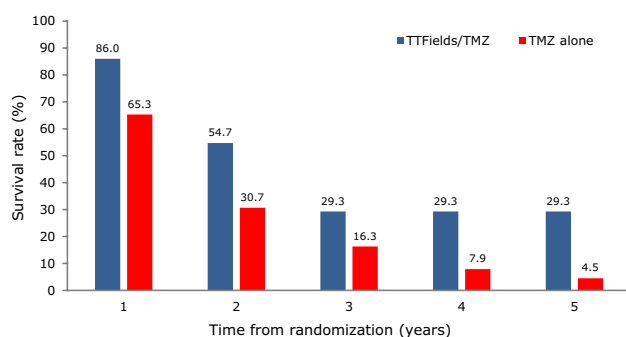
**Fig. 1** Forest plots show the effect of treatment compliance with TTFields plus TMZ on PFS and OS. A threshold value of 50% compliance with TTFields plus TMZ was needed to show a significant extension of OS compared to TMZ alone. Both PFS and OS were

extended with treatment compliance levels  $> 50\%$ . A trend in favor of longer PFS and OS was seen with higher rates of treatment compliance





**Fig. 2** Newly diagnosed GBM patients had maximal treatment benefit from TTFields plus TMZ with compliance rates >90% with a median overall survival of 24.9 months (28.7 months from diagnosis)



**Fig. 3** The annual survival rate was highest for newly diagnosed GBM patients with compliance rates >90% with a 29.3% survival rate over 5 years from randomization

(Table 2) regardless of treatment arm (reference values—compliance <75%), sex (male), resection (biopsy), *MGMT* (negative), and region (USA).

## Discussion

In this subgroup analysis of EF-14 study patients receiving TTFields plus TMZ treatment, a threshold value of  $\geq 50\%$  average compliance with TTFields plus TMZ showed an extension of PFS and OS compared to TMZ alone. Further, patients with monthly compliance >90% had maximal survival benefit with a median survival of 24.9 months (28.7 months from diagnosis) and a 5-year survival of 29.3%. This effect was independent of other prognostic factors such as performance status, age, and *MGMT* methylation status.

**Table 2** Cox proportional hazards model for OS in TTFields/TMZ patients

Parameter	Parameter value	Hazard ratio	Two-sided p-value
Treatment arm	Compliance $\geq 75\%$	0.781	0.031
Sex	Female	0.800	0.069
Resection status	Gross total resection	0.789	0.202
	Partial resection	0.777	0.181
MGMT status	Methylated	0.510	<0.001
	Unknown	0.810	0.131
Region	Outside the USA	1.157	0.199
Age		1.021	<0.001
KPS		0.984	0.006

Compliance was an independent predictor of OS in the full 5-year dataset ( $\geq 75\%$  vs. <75%) [24].

Post hoc analysis of the EF-11 trial data demonstrated longer median OS in TTFields treated recurrent GBM patients with a compliance rate of  $\geq 75\%$  compared to those with a <75% compliance rate (7.7 vs. 4.5 months;  $p=0.042$ ) [21]. This early analysis supported a preliminary target level for treatment compliance ( $\geq 75\%$ ) in clinical practice as well as evidence for a trend suggesting that higher levels of survival benefit were associated with increasing compliance [21]. Data from the PRiDe registry—using data from real-world recurrent GBM patients—also demonstrated improved OS with daily compliance rates  $\geq 75\%$  [23]. The results of the EF-14 sub-group analysis further support a threshold compliance rate of  $\geq 75\%$  for a survival benefit when compared to a compliance rate of <75% in newly diagnosed



GBM patients treated with TTFields plus TMZ. This study demonstrates that a minimal compliance threshold of > 50% with TTFields plus TMZ treatment correlated with significantly improved survival outcomes compared to TMZ alone for newly diagnosed GBM. TTFields were administered to GBM patients with recurrent disease as monotherapy in the EF-11 study and as combination therapy with TMZ in newly diagnosed GBM patients in the EF-14 study. The earlier disease stage and combined treatment may account for the survival benefits seen at a lower minimal compliance threshold in this subgroup analysis of the EF-14 study.

A variety of social and clinical factors contribute to patient compliance with TTFields therapy. Though TTFields are non-invasive and the Optune device is designed to preserve patient functioning during daily activities, initiating TTFields therapy requires some lifestyle modifications when compared to RT or systemic therapies. Some patients may be reluctant to comply with the head shaving required with every array change and wearing the arrays on a shaved head may make some patients self-consciousness, calling attention to their condition [28]. Healthcare providers experienced with TTFields therapy can provide patients assistance with incorporating the therapy in their daily life [28].

TTFields, like oral cancer treatment regimens, are administered in the home and outpatient setting and places the burden of compliance on the patient and their caregivers. Patient, healthcare provider, and treatment related factors can contribute to improved adherence or compliance with oral cancer therapy regimens [29]. Patient related factors include physical limitations, psychological, and social issues such as religious or cultural factors and the lack of a support system. The healthcare provider can also negatively influence compliance with therapy through poor communication and relationship with the patient, as well as failing to optimally select appropriate patients for oral cancer therapy regimens [29].

A good home support system is critical when considering TTFields therapy for a GBM patient [28]. A patient should have at least one support person who can assist with the Optune device operation, assist with managing adverse events, scalp maintenance and array placement. Patients with cognitive issues or poor performance status have been suggested to be more likely to be less compliant with TTFields treatment without home support [28]. However, the current study showed compliance to be independent of KPS and age as a predictor of PFS and OS, contradicting this suggestion. Treatment-related factors influencing compliance include complex treatment regimens, concomitant treatments and side effects. TTFields are not associated with systemic side effects and are less likely to affect concomitant systemic therapy.

The most common side effect in clinical trials was skin irritation for patients treated with TTFields [20, 24, 25].

Dermatological adverse events were the most common adverse events associated with TTFields; 52% of TTFields plus TMZ patients in the EF-14 trial reported mild to moderate skin irritation [24]. Skin irritation is due primarily to the nearly continuous contact of the transducer arrays with the patients shaved scalp between array changes. These events include allergic and irritant dermatitis, mechanical lesions, ulcers and skin lesions [30]. However, most of these dermatological AEs can either be prevented with proper shaving techniques, skin care and array relocations, or treated with appropriate topical regimens as required [30]. Effective skin care strategies can maximize compliance with TTFields therapy and maintain patient QoL over the course of treatment.

A limitation of this study is that it is based on a subgroup analysis of the phase 3 EF-14 trial, and inherently subgroup analyses are prone to type I errors limiting the veracity of the results [31]. In this instance, the subgroup analysis was prespecified in the protocol. However, the results of this investigation corroborate the results of similar analyses of prior clinical investigations [21–23].

## Conclusions

In this subset analysis of the EF-14 trial, a compliance threshold of 50% with TTFields plus TMZ treatment correlated with significantly improved outcomes compared to TMZ alone. Higher levels of treatment compliance with TTFields plus TMZ were associated with increased durations of progression free- and overall-survival suggesting a dose response mechanism for TTFields. This effect was independent of other prognostic factors such as performance status, age, and *MGMT* methylation status. Patients with compliance over 90% had a median survival of 24.9 months (28.7 months from diagnosis) and a 3-, 4-, and 5-year survival of 29.3%. This plateau effect on long term survival has been identified in other GBM treatments which have known immunologic mechanisms of action [32, 33]. The importance of compliance with TTFields therapy in real world clinical settings should be strongly conveyed to patients by their treating physicians and other allied healthcare providers.

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## Compliance with ethical standards

**Conflict of interest** S. A. Toms, C. Y. Kim and G. Nicholas have nothing to disclose. Z. Ram reports a research grant (principal investigator



and consultant) with Novocure, Ltd. and ownership interest (stock) in Novocure, Ltd.

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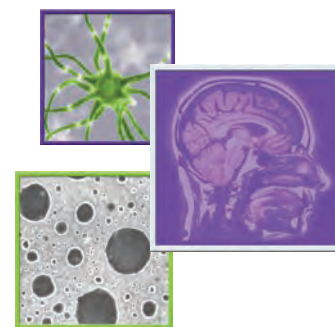


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# A state-of-the-art review and guidelines for tumor treating fields treatment planning and patient follow-up in glioblastoma



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## Practice Points

- Tumor treating fields (TTFields) in combination with temozolomide are a standard treatment option in patients newly diagnosed with glioblastoma (GB) following maximal surgical debulking and completion of concurrent chemoradiation.
- Treatment planning using the NovoTAL software optimizes TTFields intensity delivered in two orthogonal directions to the gross tumor volume and the proximal peritumoral brain zone.
- Sequential neuroimaging should be reviewed in order to assess the extent of active, residual enhancing and nonmeasurable tumor when performing treatment planning.
- Treatment should be planned mapping closely to the boundaries of active tumor or to the margins of a resection cavity visualized in axial and coronal planes using T1 postcontrast or T2/fluid-attenuated inversion recovery sequences as appropriate.
- Changes in neuroimaging can occur following the initiation of treatment with TTFields. Response assessment should incorporate a comprehensive evaluation of the patient's clinical status, concurrent therapies received, treatment compliance and general scalp health when assessing clinical response.
- The median duration of TTFields therapy in a pivotal Phase III study conducted in newly diagnosed GB patients was 9 months, with patients remaining on TTFields with a change to second-line chemotherapy through first progression.
- Treatment can be re-planned if there are significant changes in imaging from baseline.
- The development of TTFields treatment planning and response assessment algorithms aim to help standardize patient care across specialties and institutions caring for patients with GB.

Tumor treating fields (TTFields) are an integral treatment modality in the management of glioblastoma and extend overall survival when combined with maintenance temozolomide in newly diagnosed patients. Complexities exist regarding correct selection of imaging sequences with which to perform TTFields treatment planning. Guidelines are warranted first, to facilitate treatment planning standardization across medical disciplines and institutions, to ensure optimal TTFields delivery to the tumor and peritumoral brain zone while maximizing

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patient safety, and also to mitigate the risk of premature cessation of a potentially beneficial treatment. This summary guideline outlines methods for starting patients on TTFields, for monitoring patient response to therapy and provides a framework for evaluating when therapy should be re-planned, based on the extent of sequential imaging changes.

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## KEYWORDS

• alternating electric fields  
• glioblastoma • guidelines  
• NovoTAL • response  
assessment • treatment  
planning • TTFields • tumor  
treating fields

## Background

Tumor treating fields (TTFields) are an integral modality in the management of patients with newly diagnosed and recurrent glioblastoma (GB), in addition to surgery, radiation and chemotherapy. TTFields are a regionally delivered treatment utilizing alternating electric fields to disrupt highly orchestrated intracellular processes necessary for successful cell division [1–5]. TTFields are clinically delivered in paired orthogonal directions, left–right and anterior–posterior, using Optune™ (NovoTTF-100A System). Optune is a portable medical device consisting of a TTFields generator, custom backpack and insulated ceramic discs called transducer arrays, which are applied directly to a patient's shaved scalp (Supplementary Figure 1) [6,7]. The device is preset to deliver TTFields at a frequency of 200 kHz and is operated by the patient independently. It is monitored periodically by device specialists, who are available 24/7 to provide technical support to the patient, their family and physician.

TTFields are nonionizing and are delivered at an intermediate frequency (200 kHz for GB) and low intensities (1–3 V/cm) leading to a variety of downstream, antimitotic biologic effects, sparing quiescent cells. These include disruption of normal mitotic spindle and cytokinetic contractile band assembly [1,4], mitotic arrest [8], dielectrophoresis of charged intracellular macromolecules during cytokinesis [9,10], which ultimately result in polyploidy and aneuploidy in cellular progeny, leading to a loss of clonogenic potential [4,11,12], and immunogenic cell death [13]. When applied to GB cell lines in *in vitro* studies, TTFields can also induce other stress effects potentially culminating in the activation of immune-mediated and other death pathways [4,11,14]. In addition, TTFields have also been shown to induce autophagy, and can modulate cellular propensity to migrate and invade adjacent tissues [15,16]. Preclinical studies in GB and other cancer cell lines demonstrate that incremental cytotoxic effects can be

observed when TTFields' intensity is increased from 1 to 2–3 V/cm, with complete arrest of cellular proliferation observed with field intensities exceeding 2.25 V/cm [1,5]. TTFields exert maximal effects when aligned to a cell's mitotic axis. As a cell's mitotic axis can occur randomly in any direction, additive cytotoxic effects are also observed when TTFields are applied in multiple sequential directions [5].

Although the direct measurements of TTFields intensities delivered to the brain are not performed routinely, advanced electric field simulation studies can provide insights into the behavior and distribution of TTFields in the clinical setting. Spatial distributions of electric fields within the brain parenchyma have been determined in realistic head models computed with finite element method (FEM) simulations [17,18]. Image segmentation initially separates major tissue types such as scalp, skull and gray and white matter using MRI sequences and then model transducer arrays are positioned directly on the scalp [18]. The dimensions and separation of model electrodes accurately represent the geometry of ceramic discs used clinically. Volume meshes are generated and solved using the FEM framework with preset electric field parameters of 200 kHz, and isotropic tissue conductivity and relative permittivity values. A corresponding electromagnetic wavelength for a propagating field at a similar frequency would be on the order of 1 km. As TTFields are applied across the head at much shorter distances (~20–30 cm), it is not possible to precisely focus the field to target discrete structures, as is possible with radiosurgery. Instead, TTFields will distribute nonuniformly mainly throughout the supratentorial brain. Electric field intensities can differ significantly based on the heterogeneous dielectric tissue properties of cranial structures such as the gray matter, white matter tracts and cerebrospinal fluid [17–19], tumor location, tumor properties and transducer array layout [20]. As the majority of GB will recur at the margin of a resection cavity or within the proximal 20 mm



of peritumoral brain zone (PBZ) to the original tumor bed [21-23], it is important to understand the distribution of TTFields in these regions. Recent simulation studies have shown that electric field intensity delivered to the gross tumor volume (GTV) and proximal PBZ exceeds therapeutic thresholds of 1 V/cm in both orthogonal directions for models with solid brain tumors (Supplementary Figure 2) [24].

In clinical practice, TTFields are indicated in combination with maintenance temozolomide (TMZ) for the treatment of patients with newly diagnosed GB, and as monotherapy for patients with recurrent disease [25,26]. TTFields gained US FDA approval for newly diagnosed GB patients based on the positive results of the Phase III randomized controlled, EF-14 study [25]. At the first prespecified interim analysis, this trial demonstrated that 315 patients with newly diagnosed GB (who had undergone maximal surgical debulking followed by six cycles of concurrent chemoradiation), randomized 2:1 to receive TTFields with maintenance TMZ, experienced a significantly longer median progression-free survival (PFS) and median overall survival (OS) compared with patients receiving maintenance TMZ alone (20.5 vs 15.6 months; hazard ratio [HR]: 0.64;  $p = 0.004$ ). The addition of TTFields to standard of care did not increase serious adverse events and did not impair performance status or quality of life [27]. In the EF-14 study, patients randomized to the TTFields/TMZ treatment arm could remain on TTFields at first progression and switch to second-line chemotherapy [25]. In a *post hoc* analysis, OS was significantly higher from first progression, in patients receiving TTFields in combination with second-line chemotherapy compared with patients receiving second-line chemotherapy alone (11.8 vs 9.2 months; HR: 0.695;  $p = 0.0489$ ) [28]. TTFields were originally approved in the recurrent GB setting as monotherapy, based on the results of the randomized controlled Phase III, EF-11 study [26]. This randomized trial demonstrated equivalent efficacy (median OS: 6.6 vs 6.0 months; HR: 0.86;  $p = 0.27$ ) combined with improved safety and quality of life in patients receiving TTFields monotherapy compared with patients receiving best physician's choice of chemotherapy [26]. As TTFields are a locally directed therapy with no half-life, systemic side effects observed with chemotherapy are not typically seen in patients receiving TTFields monotherapy. The most

common treatment-related adverse events are dermatologic in nature and have been reviewed in detail previously [29]. Skin irritation can occur beneath the transducer arrays as a consequence of chemical irritation from the hydrogel, local moisture at the skin surface or due to allergic irritation in response to the hydrogel and adhesive tape. In addition, as treatment requires shaving of the scalp and replacing the transducer arrays two- to three-times per week, mechanical trauma from repeat shaving and physical stresses from removal and reapplication of the arrays can also predispose the skin to erosions. Pressure from the ceramic transducer discs can lead to decreased skin perfusion, a risk that is exacerbated in the presence of scars, hardware and in patients who have received prior radiation therapy. In some cases, this can lead to the development of an ulcer. Inappropriate scalp care can also lead to skin infections and folliculitis. The majority of dermatologic adverse events are mild to moderate in nature and can be managed with high-potency topical steroids or topical antibiotics without requiring breaks in treatment. Grade 3/4 adverse events were observed in 2% of patients receiving TTFields monotherapy in the EF-11 trial [26]. The TTFields device is contraindicated in patients with active implanted electronic medical devices such as deep brain stimulators, pacemakers and programmable shunts, and in patients with skull defects such as a missing bone flap, due to the risk of skin toxicity and tissue damage. It should also not be used in patients with known hypersensitivity to conductive hydrogels or in patients with infratentorial disease.

In order to maximize the intensity of electric field delivered at the site of active tumor, treatment is individualized for each patient using the Novocure Transducer Array Layout – NovoTAL™ System (NovoTAL) [30]. In simulation studies, personalizing treatment results in near doubling of TTFields intensity delivered to the GTV compared with TTFields delivery using a default symmetric array layout [20]. Treatment planning with NovoTAL is required for any patient commencing treatment with TTFields. In the clinical trial setting, treatment planning was historically performed by the study sponsor's clinical team using the patient's baseline MRI results. In the clinical practice setting, physicians certified to prescribe TTFields who are managing patients with GB, may elect to perform their own treatment planning by



completing a NovoTAL certification program, presently only available in the USA. This program provides education on the fundamental principles of electric field distribution theory and practical training on obtaining head morphometric measurements, as well as tumor coordinates from MRI scans. A basic requirement for this certification is that physicians have familiarity with reading and interpreting neuroimaging. As the treating physician may have comprehensive information regarding the patient's clinical history, current clinical status and knowledge of sequential imaging changes, there, may be potential benefits for the patient(s) in having their treating physician plan therapy directly.

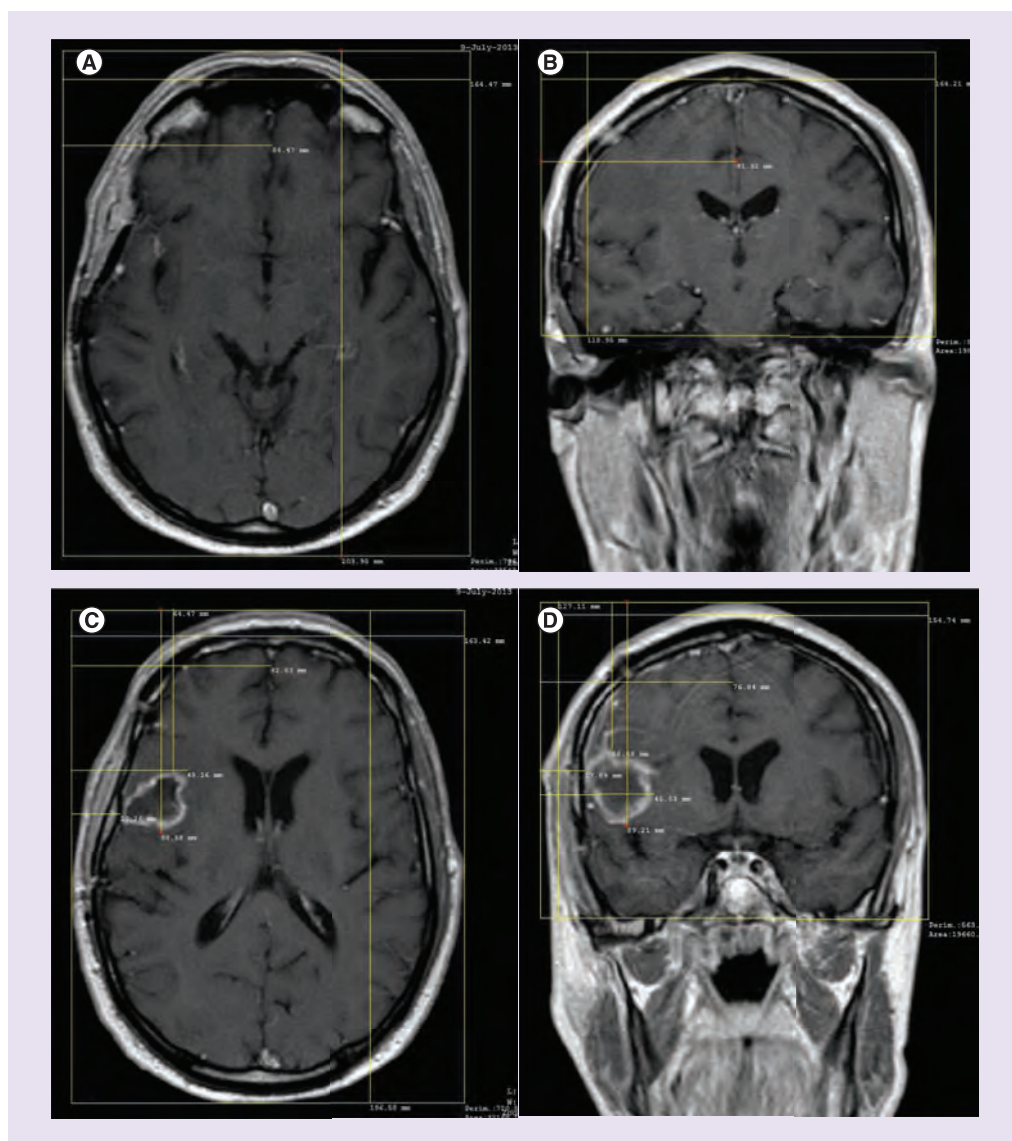
#### • Overview of TTFields treatment planning using NovoTAL

Conventional treatment mapping using the FDA-approved NovoTAL software [30] is performed by planning treatment to the extent of contrast-enhancing disease most indicative of active tumor (methods described previously) [30–33]. A measure of axial head size is first obtained using the image at the uppermost limit of the orbit on a T1-weighted sequence (Figure 1A). A fiducial frame is placed around the head bordering the outer margin of the scalp on four sides. Measurements for anteroposterior (A-P), right-to-left (R–L) and right to anatomic midline distances are obtained from the level of the scalp, extending tangentially from a right-anterior marker origin. Coronal head size is assessed in a similar manner, using a box drawn around the head to the lower margin of cerebrum on an MRI image at the level of the external auditory canal (Figure 1B). Conventional tumor location measurements are obtained from T1-weighted postcontrast sequences in axial and coronal views, selecting images that contain the maximal diameter of contrast enhancement. Boxes are drawn around the head commencing at the outer margin of the scalp axially and encompassing the extent of supratentorial cerebrum coronally. The same measurements described previously (anteroposterior, R–L and right to midline) are obtained (Figure 1C & D). In addition, four measures for tumor coordinates are obtained commencing from the reference frame and from a right-anterior or right-superior origin, respectively. On axial views, these are measurements from the right reference frame to the near tumor margin and to the far tumor margin, and the distance from the front of the

reference frame to the near tumor margin and to the far tumor margin. On the coronal slice capturing the maximal diameter of contrast enhancement, the four tumor coordinates are measured from the right reference frame to near tumor margin and to the far tumor margin, and from the top of the reference frame to the near tumor margin and to the far tumor margin. All measurements are rounded to the nearest millimeter and are entered sequentially into the NovoTAL software. Based on the data derived from FEM simulations, the software algorithm will calculate the optimal transducer array layout, which will maximize TTFields intensity at the site of the tumor based on the patient's cranial morphometry.

Although the process described above is based on MRI measurements obtained from postcontrast imaging, in the clinical setting gliomas can be very heterogeneous in nature, and thus the extent of active disease may not exclusively be captured in postcontrast sequences [34–36]. GBs may present with non-CE (NCE) T2-weighted/fluid-attenuated inversion recovery (FLAIR) signal, or more commonly may be represented in a combination in contrast-enhancing and NCE frames. A patient will minimally require an MRI with T1-weighted, T2-weighted/FLAIR and gadolinium-enhanced sequences in axial and coronal planes for treatment planning. A combination of these sequences can be used for planning purposes, as deemed appropriate by the treating physician. Although mapping based on discrete regions of contrast enhancement may result in a more focal planning approach, incorporation of margins of macroscopically normal brain or of wider regions of T2/FLAIR abnormality can alter the intensity of TTFields in areas where GB most commonly recurs such as the GTV, tumor margin and PBZ [21]. Maximizing field intensity within these zones could prove to be crucial for prolonging PFS and for improving patient outcomes overall. The PBZ, which macroscopically and radiologically resembles normal tissue, frequently harbors infiltrating tumor cells, tumorigenic stromal cells and pro-inflammatory cells, which collectively support local tumor recurrence [22]. As such, a physician may theoretically wish to include a wider margin on NCE tissue into the treatment plan for TTFields in order to treat residual infiltrating tumor cells. Results of treatment planning simulation studies exploring the inclusion of a margin of macroscopically normal tissue around





**Figure 1. Standard T1-weighted postcontrast MRI measurements required to perform NovoTAL treatment planning.** (A) An axial slice at the apical level of the orbit. A reference frame is drawn at the level of the scalp, and measurements for anteroposterior, left-right and right to midline are drawn. (B) A coronal slice at the level of the external auditory canal used to estimate the extent of cerebrum. A reference frame is drawn from the level of the scalp to an inferior boundary at the lower extent of temporal lobe, and measurements for right-left, right to midline and superior to inferior boundary are obtained. (C) Axial tumor coordinates drawn on a slice demonstrating the maximal tumor diameter. The same frame and initial measurements are repeated. In addition, measurements from the right frame to near and far tumor margins, as well as the anterior frame to near and far tumor margins, are added. (D) Coronal tumor coordinates drawn on a slice depicting the maximal diameter of tumor. The lower boundary of the box is drawn at the lowest level of visible supratentorial brain. The three initial head size measurements are repeated. In addition, measurements from the right frame to the near and far tumor margins, and from the top of the frame to the near and far tumor margin are obtained.

a boundary of contrast-enhancing tumor suggest that field intensity is optimized in the GTV and PBZ, when treatment is planned mapping

to the border of contrast-enhancing disease, as opposed to mapping to include wider margins of NCE PBZ. As such, this guideline recommends



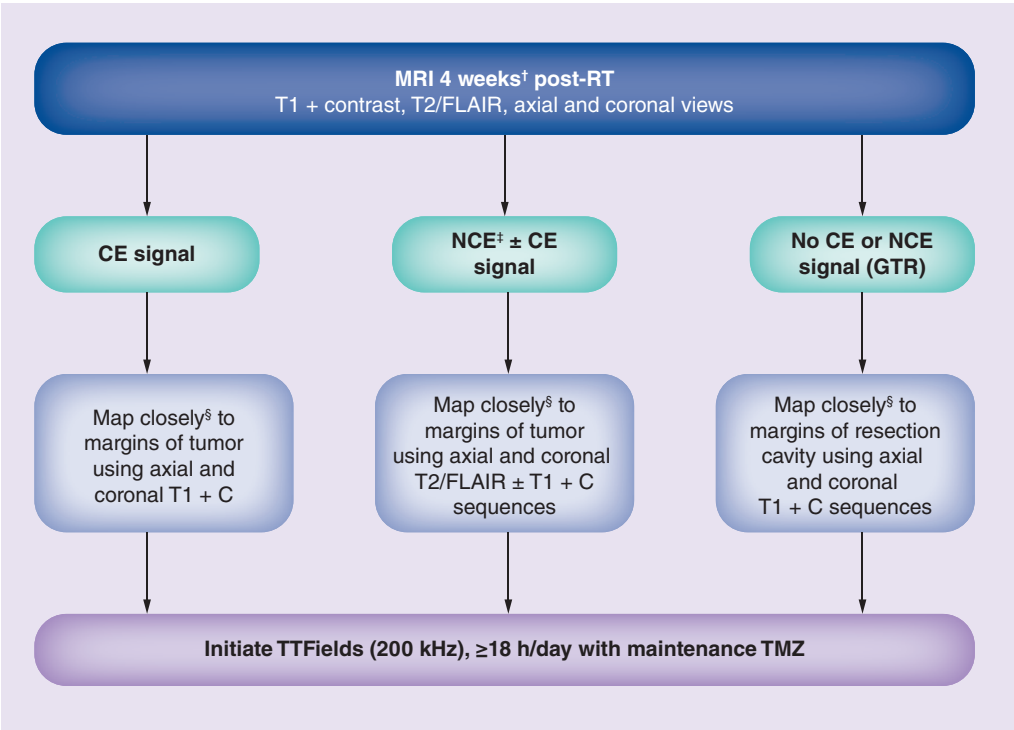
planning therapy as closely as possible to the margins of areas representing active tumor.

• **Treatment planning for newly diagnosed GB**

In the newly diagnosed setting, an MRI performed approximately 4 (range: 2–6) weeks following completion of chemoradiation should be used for TTFields treatment planning purposes. However, supplemental information from the preoperative, postoperative and preradiation therapy scans (when available) can also help inform the region most likely to represent residual active tumor and target any microscopic disease. The minimum MRI sequences required are precontrast T1, T2/FLAIR and postcontrast T1 (axial and coronal), and the recommended

slice thickness is  $\leq 5$  mm with no gap. In rare instances, where a patient cannot undergo MRI, a CT scan with contrast can be used for treatment planning, as long as axial and coronal head size and tumor position can be clearly delineated. **Figure 2** describes the algorithm for treatment planning in patients with newly diagnosed with GB.

In the postradiation setting, an important consideration is to distinguish post-treatment imaging changes such as pseudoprogression [37,38] from true disease progression. As mentioned previously, field intensity will be maximized in the GTV and PBZ, when the field is mapped as closely as possible to the margin of active tumor, so care should be taken not to overestimate the extent of active residual tumor. As reactive



**Figure 2. Tumor treating fields treatment planning algorithm for newly diagnosed glioblastoma.**

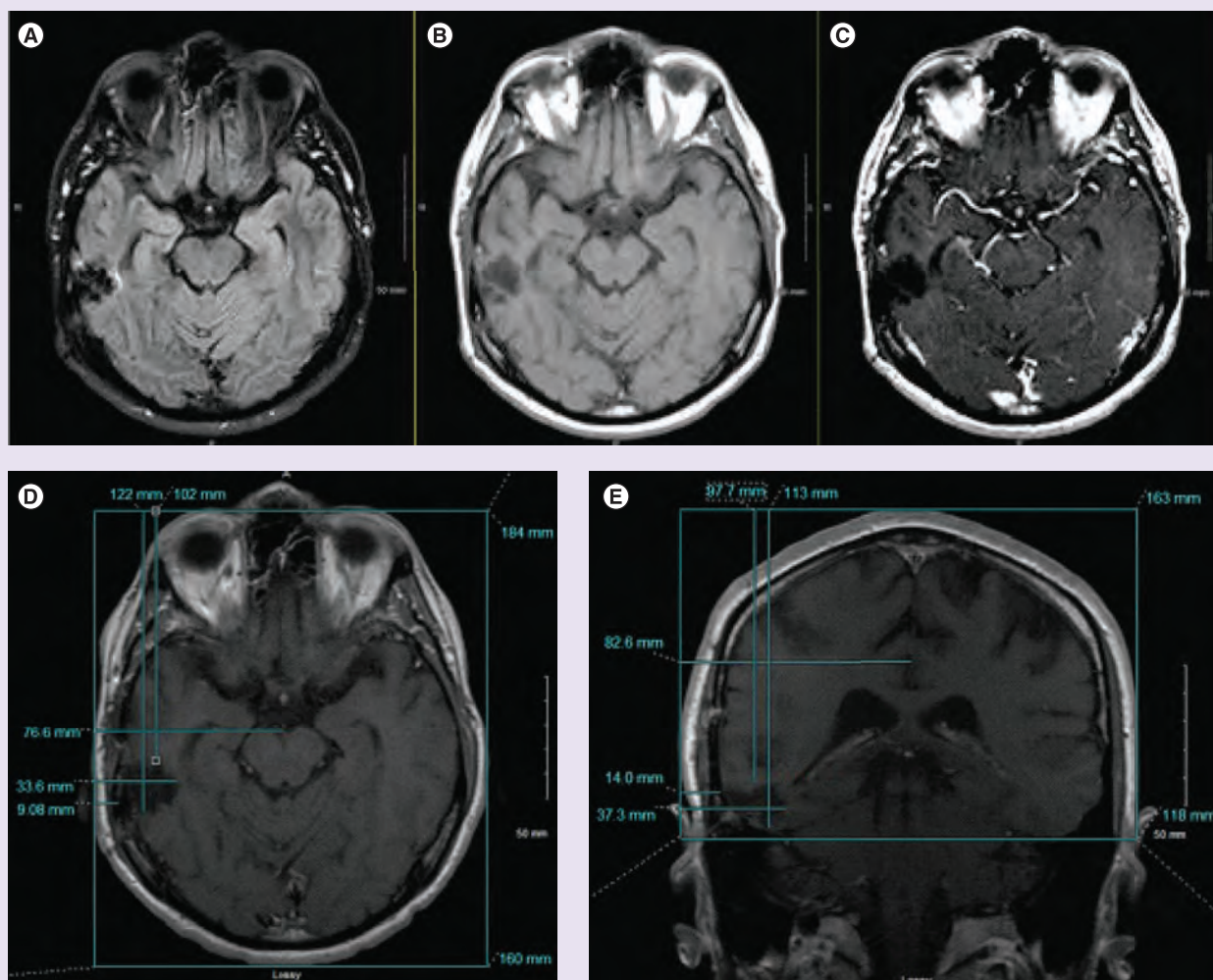
<sup>†</sup>MRI obtained 2–6 weeks following completion of concurrent chemoradiation is recommended for treatment planning in patients with newly diagnosed GB. Where available, compare preoperative and pre-RT sequences to determine areas of active disease versus post-treatment sequelae.

<sup>‡</sup>In instances where a newly diagnosed patient has exclusively NCE signal, mapping should be performed using axial and coronal T2/FLAIR images, closely approximating to the margins of the tumor.

<sup>§</sup>Coordinates for tumor location should closely approximate the edge of the region most representative of active tumor without including extra margin of normal tissue. This approach will maximize the field intensity in both the tumor volume and proximal peritumoral brain zone.

C: Contrast; CE: Contrast enhancement; FLAIR: Fluid-attenuated inversion recovery; GTR: Gross total resection; NCE: Noncontrast enhancement; RT: Radiotherapy; TMZ: Temozolomide.





**Figure 3. Treatment planning in patient post gross total resection with no evidence of residual disease.** (A–C) (from top left to right) Post-radiotherapy axial views on fluid-attenuated inversion recovery, T1 and T1 with contrast sequences for a patient post-gross total resection. Head size measurements are obtained as standard on slices at the apical level of the orbit on axial views and at the level of the auditory canal on coronal views (not shown). (D & E) Treatment planning to the boundaries of the resection cavity on axial and coronal views, respectively. On axial views, the reference frame is drawn around the head, excluding the nose anteriorly. On coronal slices, the reference frame is drawn at the level of the scalp, excluding the ears, and the inferior margin is drawn to the lowest level of visible tentorium.

alterations in the blood–brain barrier with contrast enhancement may mimic tumor progression, there may be clinical value in obtaining additional imaging such as a magnetic resonance perfusion or PET scan in order to determine which areas represent active tumor [39–41]. For patients who have undergone a gross total resection and have neither residual contrast-enhancing nor NCE signals, treatment planning should be performed mapping as closely to the margins of the resection cavity as possible (Figure 3). The output from the NovoTAL software – the transducer array layout map – should subsequently be

evaluated in the context of any surgical scars, impaired skin or palpable hardware that may impact the application of the transducer arrays on the patient’s scalp. TTFields are contraindicated in patients with skull defects where the bone was not replaced and the arrays should not be placed directly above any palpable hardware, screws or underlying serious skin condition. A slight shifting of the arrays is appropriate in such instances.

In patients who have undergone biopsy or subtotal resection (those with residual tumor), sequential scans should be reviewed to determine



the areas that represent most active areas of tumor. Mapping should be performed using the postcontrast and/or T2/FLAIR sequences as appropriate. The size of the planning field should conform to the boundary of active tumor, avoiding and excluding blood products or cystic cavities not surrounded by active tumor, in order to optimize the field intensity in the tumor volume and PBZ.

#### • Treatment planning for recurrent GB

There are additional practical considerations when planning treatment with TTFields for patients with recurrent GB, again with regard to evaluating and interpreting imaging changes and assessing the effects of prior therapies. Tumor progression can often be challenging to distinguish from pseudoprogression [42] or radiation necrosis. Given the frequent use of bevacizumab in recurrent GB, pseudoresponse should also be carefully evaluated in patients receiving antiangiogenic therapy [37,43-44]. These scenarios can lead to both an over- or under-estimation of active tumor volume in the context of TTFields planning and may lead to suboptimal delivery of TTFields. In this setting, additional information obtained from advanced imaging modalities such as diffusion-weighted imaging, apparent diffusion coefficient maps, magnetic resonance spectroscopy and perfusion-weighted imaging may help correlate regions that represent active tumor and distinguish tumor from pseudoprogression [45,46]. Patient's scalp health should also be carefully evaluated when considering TTFields in the recurrent GB setting. Prior exposure to systemic chemotherapies and radiation may render patients more susceptible to skin toxicity (the most common device-related adverse event reported with TTFields treatment); therefore, regular evaluation of the patient's scalp while receiving therapy can help prevent the development of local skin irritation beneath the transducer arrays [29]. **Figure 4** describes the algorithm for treatment planning in patients with recurrent GB. The most recent MRI scan showing tumor progression should typically be used for TTFields treatment planning in patients with recurrent GB. A careful comparison between prior scans should be made in order to identify the areas of active tumor. This is especially important in patients who have received antiangiogenic therapy, in whom prior imaging (when available) should be evaluated with the most recent scan. Many

patients receiving bevacizumab commonly progress with a nonenhancing signal abnormality and therefore are more likely to require the inclusion of T2/FLAIR sequences in treatment planning. The treating physician should correlate the imaging findings with the patient's clinical status and determine the region where the TTFields should be focused. The mapping coordinates should conform closely to the margin of the active tumor as this will maximize field intensity in the tumor volume and the PBZ (**Figure 5**).

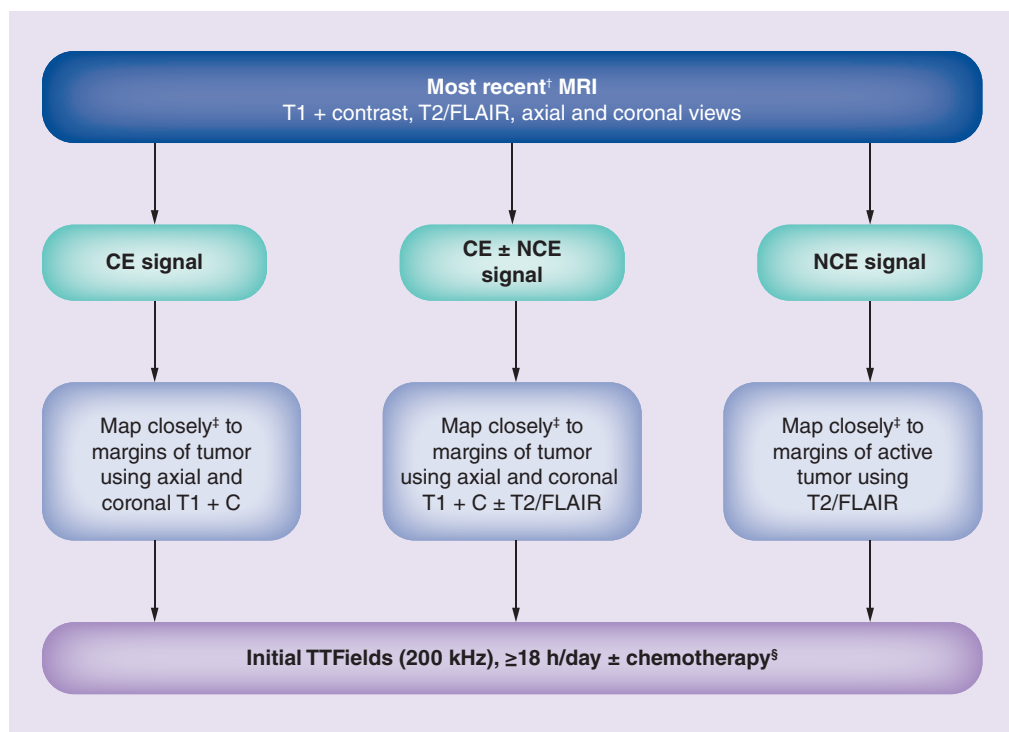
#### • Treatment planning for multifocal GB

Approximately one in five patients with GB may present with multifocal or multicentric disease manifesting with assorted distinct foci of enhancing tumors [47]. TTFields are a viable modality in the treatment of such patients, as TTFields distribute at therapeutic intensities within large areas of the supratentorial brain [17]. The NovoTAL software can accommodate treatment planning for any number distinct lesions (>1 cm apart) within its algorithm. Any lesions which are <1 cm apart should be treated as one contiguous lesion. The approach to planning therapy in cases with multifocal disease is the same as described previously; once measurements for axial as well as coronal head size have been obtained, each lesion should be delineated and measured separately, and the coordinates entered sequentially into the NovoTAL software (**Figure 6**).

#### • Response assessment & remapping TTFields

Once TTFields are initiated, the treating physician should monitor the patient's monthly compliance report to ensure that patient is receiving the maximal benefit from the treatment (the recommended goal is to be on therapy >18 h per day), and should periodically assess the scalp so that any local skin irritation is appropriately managed. A follow-up MRI scan should routinely be performed 2–3 months following treatment start as is the standard practice for GB follow-up. There are unique challenges associated with the ongoing evaluation and interpretation of imaging changes in response to treatment with TTFields, which are compounded by observations from clinical trials suggesting that there is no definitive correlation between objective radiographic response and overall patient benefit. *Post hoc* analyses have





**Figure 4. Tumor treating fields treatment planning algorithm for recurrent glioblastoma.**

<sup>†</sup>Where available, compare pretreatment and post-treatment imaging to determine areas of active disease versus post-treatment sequelae, especially in patients receiving antiangiogenic therapy.

<sup>‡</sup>Coordinates for tumor location should closely approximate the edge of the region most representative of active tumor without including extra margin of normal tissue. This approach will maximize the field intensity in both the tumor volume and the proximal peritumoral brain zone.

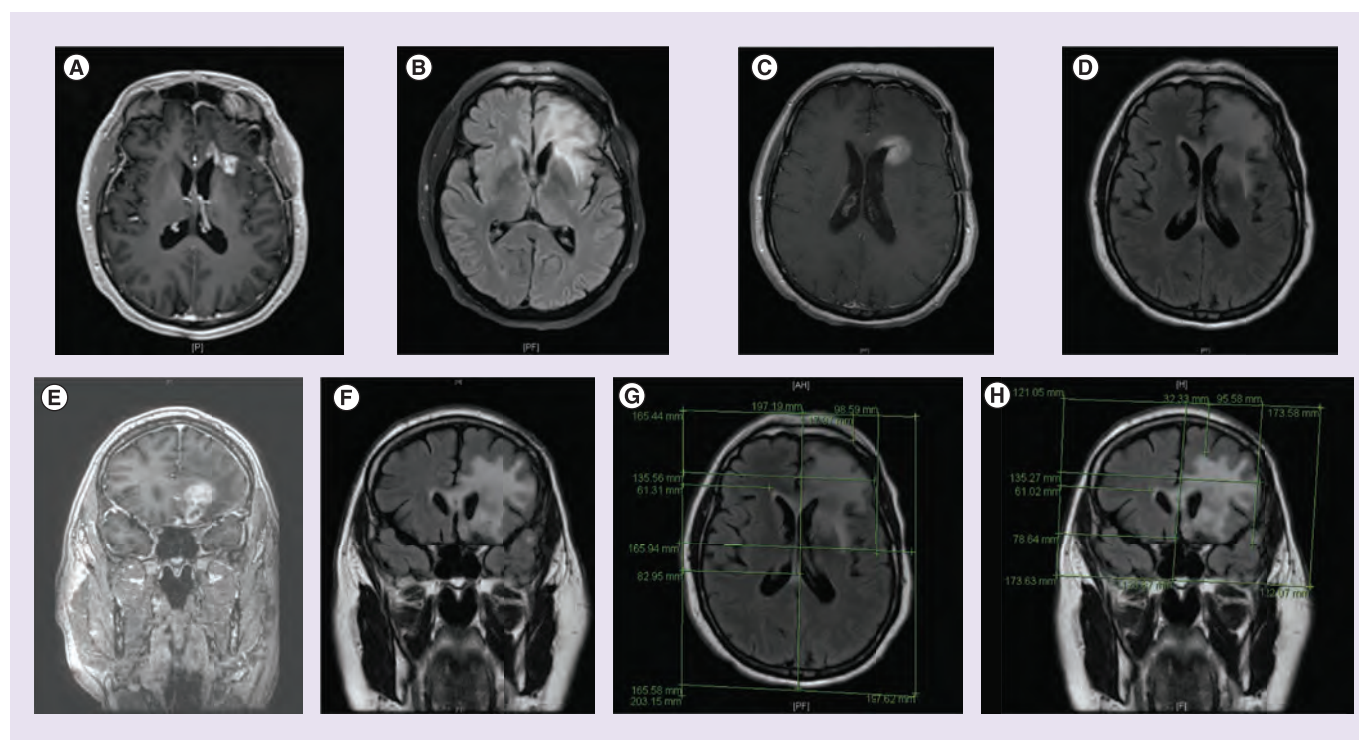
<sup>§</sup>Patients initially receiving TTFields with maintenance TMZ who experience first progression, can remain on TTFields with a change to second-line chemotherapy.

C: Contrast; CE: Contrast enhancement; FLAIR: Fluid-attenuated inversion recovery; NCE: Noncontrast enhancement; TMZ: Temozolomide.

demonstrated that tumor regression and clinical benefit can still occur following initial early radiographic progression in patients receiving TTFields [48,49]. In a *post hoc* responder analysis from EF-11 (where TTFields were administered as monotherapy in recurrent GB patients), approximately a third of responders experienced progressive disease on their 2-month scan following initiation of TTFields. However, they subsequently developed delayed (median time to onset of objective response of 8 months), durable (a median duration of 7 months) and objective radiographic responses [48]. Similar observations are noted in patients receiving novel immunotherapeutics [50-52], which have recently prompted the Response Assessment in Neuro-Oncology Criteria (RANO) working group to develop an updated immunotherapy response assessment guideline (iRANO). This new guidance allows patients to remain

on immune therapy if they demonstrate initial radiographic progression in the absence of significant clinical decline [53]. The iRANO updates recognize that immune therapies may take a longer period of time to confer a clinical benefit and facilitates a mechanism to prevent patients coming off therapy prematurely in the absence of true progressive disease, while ensuring patient safety. Similarly, TTFields require a longer period of treatment (at least 4 weeks of continuous exposure) in order to reach a state of tumor stabilization during the course of therapy [49]. As TTFields exert an antimitotic effect, there will be an initial period where the rate of tumor cell replication will exceed cell killing and clearance rates from the brain. Over time, the rate of cell cytotoxicity and clearance will eventually exceed replication rates and, therefore, there will be a delay until tumor shrinkage is observed on sequential





**Figure 5. Treatment planning in a recurrent glioblastoma patient with nonmeasurable progression post-bevacizumab.**

(A & B) Preprogression axial T1 postcontrast and axial fluid-attenuated inversion recovery (FLAIR) abnormality, with no abnormality at the rostral, superior, lateral ventricle. (C–F) Postprogression axial T1 postcontrast and FLAIR abnormality, and coronal T1 postcontrast and FLAIR images. In this case, planning TTFIELDS treatment using T1 postcontrast sequences will underestimate the extent of tumor progression. (G & H) Treatment planning performed using axial and coronal FLAIR sequences, obtaining tumor coordinates to the margins of FLAIR abnormality.

imaging. In addition, early contrast-enhancing imaging changes may, in fact, represent a local inflammatory response to therapy, not necessarily overt tumor progression [54]. As such, this clinical guideline provides recommendations for maintaining and/or terminating therapy, based on a holistic assessment of the patient's clinical status, concurrent therapies and their imaging findings. Figure 7 describes the algorithm for response assessment and remapping patients receiving TTFIELDS.

As TTFIELDS do not impact the blood–brain barrier, any reduction in tumor size is indicative of a true anti-tumor effect (as opposed to pseudoresponse observed with antiangiogenic therapies). However, as TTFIELDS may be used routinely in the clinical setting in conjunction with other chemotherapies, radiographic response assessment should be evaluated per the RANO criteria. In patients experiencing a complete or partial response, or those with stable disease, it is recommended to maintain TTFIELDS therapy with the same array layout configuration. In instances where there has been

a dramatic reduction in the extent of contrast enhancement (>50% reduction) in the absence of antiangiogenic therapy, it is also feasible for the treating physician to re-map the tumor based on the latest imaging, to ensure that the field is focused to the reduced area of contrast enhancement.

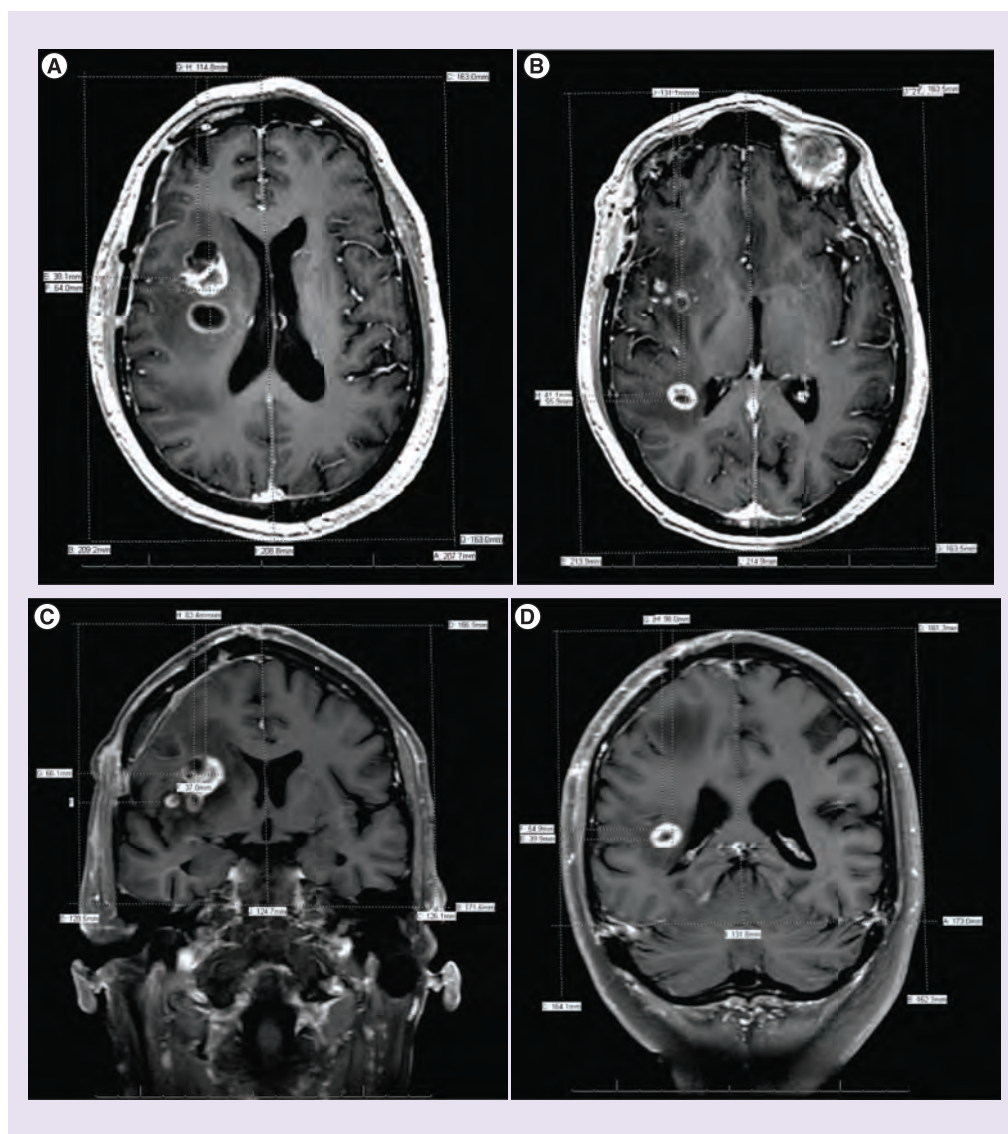
In patients exhibiting radiographic progression from the baseline planning scan, a number of factors should be considered. First, if the patient is a patient with newly diagnosed GB who has recently started TTFIELDS in combination with maintenance TMZ, and has clinically deteriorated, it is recommended to continue TTFIELDS and switch to a second-line chemotherapy as long as the patient remains compliant and able to tolerate the treatment. In the EF-14 Phase III study in patients with newly diagnosed GB, the median duration of TTFIELDS therapy was 9 months, while median PFS was 7.1 months [25], with the majority of patients in the TTFIELDS arm receiving second-line chemotherapies at first progression. If the patient has a recurrent GB and experienced



significant neurologic decline consistent with the imaging changes since initiating TTFields, then treatment should be re-evaluated at the clinician's discretion.

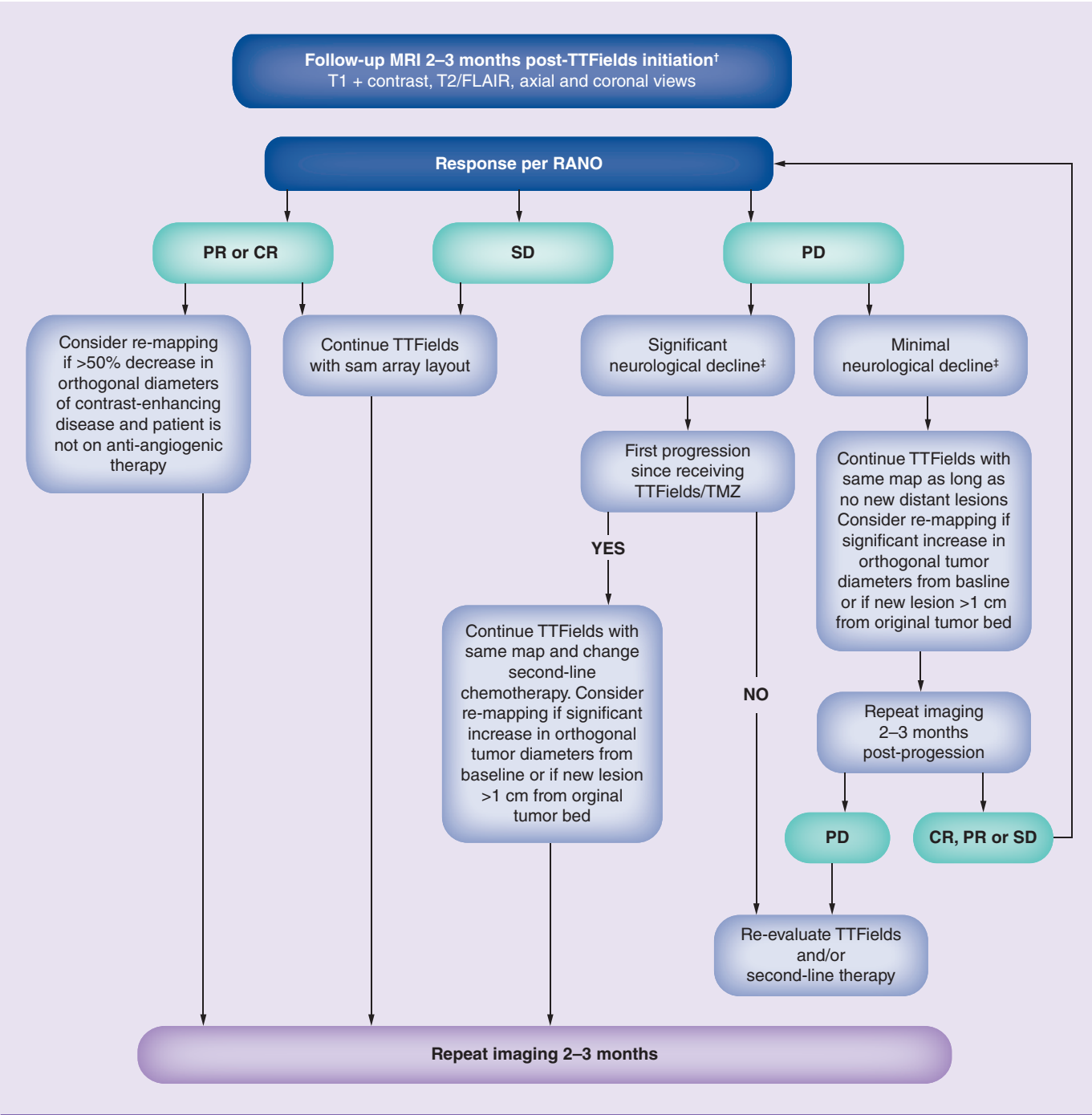
In patients who exhibit radiographic changes consistent with disease progression at the 2-month scan, but who remain neurologically stable and are compliant with therapy, it is feasible to maintain them on TTFields therapy with the same transducer array layout and repeat the scan in another 2–3 months. If however, there

appears to be a significant increase of >25% in size, or new lesions have appeared distal to the original treated tumor bed at the first follow-up scan, then it is recommended to re-plan treatment to include the new or increased size lesions in the field and then continue with therapy. In general, any major changes in imaging from the baseline planning scan should be reviewed in the context of the TTFields treatment field, and re-planning should be considered at the treating physicians' discretion. Since TTFields exert



**Figure 6. Treatment planning for multifocal tumors.** (A & B) Axial views of a multifocal tumor with a multicentric right frontoparietal lesion, and a smaller posterior lesion adjacent to the posterior horn of the lateral ventricle. (C & D) Corresponding coronal views are shown. (B & C) Treatment planning commences with a determination of head size on a slice at the apical level of the orbit and at the level of the ear canal per standard planning. Multifocal lesions are then mapped separately when >1 cm apart. The multicentric anterior lesion is mapped as one contiguous lesion.





**Figure 7. Response assessment and remapping algorithm for tumor treating fields in glioblastoma.**  
†Serves as new reference scan if TTFields treatment continued.  
‡Clinical and neurological decline indicative of tumor progression and not attributable to a co-existing medical condition.  
CR: Complete response; FLAIR: Fluid-attenuated inversion recovery; PD: Progressive disease; PR: Partial response; RANO: Response Assessment in Neuro-Oncology Criteria; SD: Stable disease; TMZ: Temozolomide; TTFields: Tumor treating fields.

an antimitotic effect exclusive to dividing cells, it may take several months of continuous use before true antitumor responses manifest on sequential imaging.

**Future perspective**  
It has been more than a decade since the anticancer effects of TTFields were first characterized in GB cell lines and clinical studies were initiated.



Today, TTFields are FDA-approved for newly diagnosed and recurrent GB and further development is underway in a variety of solid tumors [55-60]. Since TTFields are a comparatively new anticancer modality compared with surgery, chemotherapy and radiation therapy, this poses additional challenges in the clinic with regard to appropriately training physicians who are certified to plan treatment. This summary guideline proposes a framework for TTFields treatment planning that is consistent with current standards for MRI acquisition and response assessment, which are sensitive to the heterogeneity of tumor activity in imaging and which aim to maximize field intensity at the site of active tumor. Importantly, it proactively addresses early imaging changes that can occur in patients receiving TTFields which may not be indicative of disease progression. The algorithms provide clinicians a roadmap for preventing premature treatment discontinuation of a potentially beneficial modality while balancing safety. As experience with TTFields grows, this guideline will require future revisions to incorporate the integration of advanced imaging modalities in treatment planning, and the potential inclusion of radiologic biomarkers to assess response to treatment. The prospective inclusion of these guidelines in future clinical studies is warranted in order to establish their clinical effectiveness.

### Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <http://www.futuremedicine.com/doi/full/10.2217/cns-2016-0032>

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# Treatment of Glioma in the 21st Century: An Exciting Decade of Postsurgical Treatment Advances in the Molecular Era



Joon H. Uhm, MD, and Alyx B. Porter, MD

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## Abstract

The past decade has brought about major changes in the way we classify and have begun to approach patients with high-grade glioma. As we trend toward personalized medicine, we are now able to utilize the molecular characteristics of each individual's tumor in order to tailor their treatment, particularly if the patient is elderly or has a poor performance status at baseline. We address the state of the practice as of 2016 in regard to chemotherapy, immunotherapy, and tumor-treating fields. The goal of this review is to enhance readers' understanding of the nuances that are allowing clinicians to tailor the treatment of high-grade glioma more specifically.

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The past decade has seen remarkable research advances in glioblastoma that have culminated in tremendous improvements in patient outcome, with extensions in overall survival that have never been

seen previously. Whereas 2-year survival for patients with glioblastoma remained stagnant for decades at a dismal 10%, it nearly tripled to 27% with the advent of temozolomide (TMZ) and increased almost 5-fold for patients



whose tumors harbor a specific genetic alteration (O<sup>6</sup>-methylguanine-DNA methyltransferase gene [MGMT] promoter methylation) in a pivotal study just over 10 years ago.<sup>1-3</sup> The publication of that pivotal study a decade ago was the beginning of one advance after another, each documenting improvements in survival for patients with gliomas. Through advances in the identification of molecular signatures found in these tumors, new directions have been identified that are guiding treatment options in the field. Such new directions include the key role of genetic alterations that will inevitably replace the standard diagnostic procedures based on microscopy (histology/grade). These genetic alterations help to better match specific treatment modalities with a tumor based on its biologic features. This article will highlight several key advances in chemotherapy that have occurred over the past decade that, in turn, direct us toward an even brighter future for our patients.

#### CHEMOTHERAPEUTIC EXTENSION OF SURVIVAL IN PATIENTS WITH GLIOBLASTOMA: TMZ AND THE IDENTIFICATION OF MGMT AS A MOLECULAR MARKER

As the field of neuro-oncology was approaching the end of the 20th century, we had amassed a wealth of information about the molecular biology of glioma cells, which, in turn, identified many potential targets for therapeutics. Figure 1 illustrates the signal transduction pathways that drive glioma growth, with several principal components: the growth factor receptor (GFR) at the cell surface functioning as a “docking station” for growth signals; secondary messenger systems within the cells that are activated by GFRs; the DNA as a common convergence point for many signal transduction pathways to activate expression of cancer-associated genes (oncogenes); and the protein products of those oncogenes that then define the malignant phenotype (cell cycle progression/mitosis, angiogenesis, tumor invasiveness).<sup>1</sup> Each component of this molecular diagram is an ongoing or potential target for therapeutics. Despite numerous drugs developed to inhibit the new molecular targets of signal transduction, in the end it was targeting DNA—the archetypal target in most cancers—that led to the first chemotherapy breakthrough with the advent of TMZ.<sup>2,3</sup>

The benefit of TMZ is summarized in Table 1. For decades, the dogma held that surgery<sup>4</sup> and radiotherapy (RT)<sup>5</sup> were the only 2 therapeutic modalities that improved survival of patients with glioblastoma multiforme (GBM), with only 10% of patients surviving 2 years. A pivotal European/Canadian study by Stupp et al<sup>2</sup> described the addition of a well-tolerated oral chemotherapeutic agent, TMZ, which alkylates DNA (adds methyl group—hence the term *alkylation*—to guanine residue of DNA) (since termed the *Stupp protocol*). The Stupp protocol includes TMZ at 75 mg/m<sup>2</sup> on days 1 through 42 with concomitant RT, followed by TMZ on days 1 through 5 of 28 for 6 consecutive months as adjuvant therapy at a dose of 150 to 200 mg/m<sup>2</sup>. This regimen led to an improvement in 2-year survival to 27%. Furthermore, the presence of a specific alteration—methylation of the MGMT gene promoter—improved 2-year survival to 47%, a 5-fold increase compared with RT alone.<sup>3</sup> The MGMT gene product repairs the DNA modification caused by alkylators such as TMZ, and therefore, silencing of the MGMT gene by promoter methylation is thought to confer increased sensitivity to TMZ. As a result of these 2 back-to-back publications in 2005, RT combined with TMZ became the long-awaited new standard of care in newly diagnosed glioblastoma and MGMT the key molecular marker in our field.

#### TAILORING THE STUPP REGIMEN FOR THE ELDERLY PATIENT POPULATION

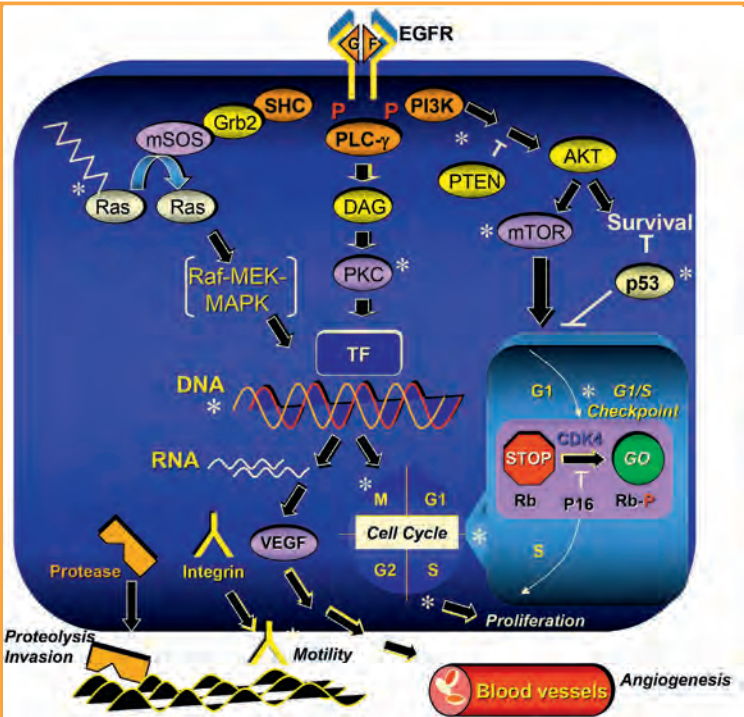
MGMT promoter methylation thus became an important prognostic marker in neuro-oncology. Given that the benefit of TMZ is most apparent when this gene alteration is present, MGMT methylation may also be a marker that guides therapy choices. The role of MGMT in helping to guide therapy was highlighted in a series of reports pertaining to optimization of treatment for the elderly population with high-grade glioma.

Table 2 summarizes the evolution of treatment—in particular, the trimming of the Stupp regimen—for the elderly patient population. The French study<sup>6</sup> found that a standard 6-week course of RT (6000 cGy over 6 weeks) improves survival compared with palliative care alone. However, the standard RT course was poorly tolerated by



many patients in the study, leading to a decrease in Karnofsky Performance Status (KPS) score, increased utilization of corticosteroids, and decreased quality of life, raising the question as to whether the standard RT course is suitable for all elderly patients. Particular concern is given to those with poor KPS score because these patients are at greatest risk for poor tolerance of RT and may be unable to complete the full course of therapy. The Canadian study<sup>7</sup> addressed this concern and documented that RT could be abbreviated to 3 weeks without compromising survival and that this regimen was, as anticipated, better tolerated. Nonetheless, the question remained as to whether RT could be omitted altogether and the patient be treated with the well-tolerated oral TMZ alone. In this regard, the subsequent German<sup>8</sup> and Scandinavian<sup>9</sup> studies found that for patients with MGMT methylation, treatment with TMZ alone was not inferior (or perhaps was even superior) to RT. These aforementioned studies evaluated specific RT schedules (without chemotherapy) or TMZ alone but did not evaluate the question of combining RT with chemotherapy. That question was addressed by the European Organisation for Research and Treatment of Cancer (EORTC)/National Cancer Information Center study<sup>10</sup> comparing abbreviated (3 weeks) RT used alone or in combination with TMZ, the latter being a “trimmed down” version of the original Stupp protocol. In a recent report, the study results were positive, with the addition of TMZ to RT improving overall survival, especially in patients with MGMT methylation.

There is no doubt that these recent reports reflect tremendous advances in our treatment options for the elderly patient population. But the results also raise important questions. For one, what age group should be defined as elderly? The patients in the aforementioned studies ranged from 60 years or older to 70 years or older. Also, what matters more—chronological age or biological age? Should all patients over a certain age be barred from a 6-week standard course of RT (which would bar them from many clinical studies)? Despite the questions raised, these recent advances arm the clinician with choices. For example, for the patient whose neurologic/performance status is somewhat compromised, a 3-week



**FIGURE 1.** Signal transduction pathways in glioma. AKT = protein kinase B or serine/threonine kinase; mTOR = mechanistic target of rapamycin; PKC = protein kinase C; PTEN = phosphatase and tensin homolog; p53 = tumor protein 53; TF = transcription factor; VEGF = vascular endothelial growth factor. \* Indicates targets for chemotherapy.

course of RT (with TMZ) is a viable option because it is likely to be better tolerated than 6 weeks of RT. For the patient whose KPS score is quite poor but treatment is still desired, then perhaps TMZ alone could be considered (if the tumor is MGMT methylated). Such diversity of choices was not previously available to this growing patient population in which adverse effects of treatment are all the more apparent than in younger age groups. Undoubtedly, incorporation

TABLE 1. Impact of Temozolomide and MGMT Promoter Methylation on Survival in Patients With Glioblastoma	
Treatment modality	2-Year survival
RT only	10%
RT + TMZ	27%
RT + TMZ + MGMT promoter methylation	47%

MGMT = O<sup>6</sup>-methylguanine-DNA methyltransferase gene; RT = radiotherapy; TMZ = temozolomide.



TABLE 2. Evolution of Treatment Options for Elderly Patients

Study	Question/study/results
Keime-Guibert et al, <sup>6</sup> 2007	<b>Question:</b> Does radiation matter? <b>Study:</b> Randomized study of standard RT (up to 6000 cGy over 6 wk) vs palliative care (patients $\geq 70$ y) <b>Results:</b> Yes. RT improved OS, but there was poor tolerance of 6-wk RT in many patients
Roa et al, <sup>7</sup> 2004	<b>Question:</b> Can RT be abbreviated? <b>Study:</b> 4000 cGy for 3 wk vs 6000 cGy for 6 wk; patients $\geq 60$ y <b>Results:</b> Yes. Abbreviated RT is not inferior to standard 6-wk course; the shortened course of RT was better tolerated as well
Wick et al, <sup>8</sup> 2012	<b>Question:</b> Can RT be omitted and TMZ used alone? <b>Study:</b> 6000 cGy for 6 wk vs TMZ alone; pts $>65$ y <b>Results:</b> Yes. In <i>MGMT</i> methylated patients, TMZ was not inferior (perhaps even superior) to RT
Malmström et al, <sup>9</sup> 2012	<b>Question:</b> How does TMZ alone compare to RT 6 wks vs 3 wks? <b>Study:</b> Comparison of 6 wk of RT vs 3 wk of RT vs TMZ alone <b>Results:</b> Abbreviated RT was not inferior to 6 wk of RT; if tumor is <i>MGMT</i> methylated, using TMZ alone is an option
Perry et al, <sup>10</sup> 2016	<b>Question:</b> Is there any benefit of adding TMZ to the abbreviated RT? <b>Study:</b> 3 wk of RT with or without TMZ; patients $\geq 65$ y <b>Results:</b> Yes. TMZ extends survival when added to 3-wk course of RT; benefits all groups, but benefit is most apparent in <i>MGMT</i> methylated patients
EORTC = European Organisation for Research and Treatment of Cancer; <i>MGMT</i> = O <sup>6</sup> -methylguanine-DNA methyltransferase gene; NCIC = National Cancer Information Center; NOA = Neuro-oncology Working Group; OS = overall survival; RT = radiotherapy; TMZ = temozolomide.	

of other genetic markers (see “A Decade of Advances in Genetics and Chemotherapy: Is Immuno-oncology the Next Frontier?” section) will further advance our understanding and tailoring of therapy for not only elderly patients but patients of all ages.

#### CAN WE FURTHER IMPROVE OUTCOME BY ADDING ANOTHER TREATMENT TO THE RT-TMZ COMBINATION?

Although the demonstration of extended survival with TMZ for patients with GBM was a tremendously welcome and long-awaited advance, we need to continue to build on this foundation. Many of the extracellular and intracellular targets illustrated in Figure 1 have been subjected to drug targeting. To date, no one drug has been found to add another layer of benefit to the RT-TMZ regimen for newly diagnosed GBM.

In the current model for clinical trials for newly diagnosed GBM, promising agents

are first tested in the setting of recurrent glioma (see “When Up-front Therapies Fail: Treatment Options for Recurrent Glioma” section) and if there is evidence of activity (for example, prolongation of progression-free survival), the drug is brought to the frontline setting for evaluation in newly diagnosed patients. In that regard, the monoclonal antibody (bevacizumab) that inhibits angiogenesis by binding and neutralizing a tumor-derived paracrine angiogenic protein (vascular endothelial growth factor [VEGF]) produced impressive results in the recurrent glioma setting.<sup>11,12</sup> However, when tested in conjunction with RT-TMZ in newly diagnosed GBM in 2 large prospective, randomized studies,<sup>13,14</sup> no benefit was seen compared with placebo added to RT-TMZ. Although these results were disappointing, some degree of optimism remains regarding bevacizumab for this patient population. Molecular analysis of patient tumor samples by microarray-based gene expression profile analysis has revealed that patients whose tumor harbors the proneural expression profile live longer when treated with bevacizumab.<sup>15</sup> Such findings underscore the importance of incorporating molecular markers into clinical trials that provide additional layers of data stratified by genetic alterations.

While the search continues for drugs or antibodies to improve outcome for patients with newly diagnosed GBM, exciting results have emerged by way of a medical device. Described as a fourth modality of therapy (the 3 conventional modalities being surgery, RT, and chemotherapy), the tumor-treating field (TTF) device was found in an open-label prospective randomized study to increase survival, boosting the 2-year survival from 29% with RT-TMZ alone to 43% when the TTF device was added in the adjuvant treatment phase in patients with a good performance status.<sup>16</sup> The TTF-based device consists of a battery/power source that is connected to adhesive pads containing arrays that generate a high-frequency alternating electric field. The proposed mechanism of action is that such a device applied to the patient's shaved head interferes with the formation of microtubules required to separate DNA during mitosis. During mitosis, tubulin monomers must undergo polymerization to



form microtubules, but in the presence of the TTF generated by the device, this polymerization is disrupted as the intrinsic electric dipole of each tubulin monomer leads it to align in the direction of the device-generated electric field,<sup>17</sup> leading to disruption of glioma cell mitosis. After its approval by the US Food and Drug Administration (FDA) in late 2015, the TTF device modality is finding its place in our armamentarium of glioma therapeutics.

#### **WHEN UP-FRONT THERAPIES FAIL: TREATMENT OPTIONS FOR RECURRENT GLIOMA**

The aforementioned advances of TMZ added to RT (Stupp regimen), tailoring of RT-TMZ to the elderly population, and abrogation of mitosis by electric fields have changed the landscape of glioma therapy. Nonetheless, for the great majority of patients with GBM, the tumor does ultimately break through frontline therapies. To date, bevacizumab remains the only treatment that has gained widespread acceptance for nonsurgical treatment of recurrent glioma. There are 2 important points about the journey leading to bevacizumab approval for recurrent glioma.

First, innumerable clinical studies evaluating drugs that target GFRs and secondary messenger system components (illustrated in Figure 1) have failed dismally. These failures are due to a myriad of reasons, including poor delivery and redundancy in the signaling system. Delivery of many of these drugs, which are often hydrophilic/polar in nature, is severely impeded by the blood-brain barrier,<sup>18</sup> and hence, effective drug concentrations often cannot be attained.<sup>19,20</sup> Moreover, even if a drug were able to traverse the blood-brain barrier and neutralize its intended GFR target, the tumor cell may not be affected because other GFRs that are also overexpressed continue to drive tumor growth.<sup>21,22</sup>

Second, given the poor experience in targeting specific signaling pathway components in glioma, would better results be attained by targeting an aspect of tumor biology that is not unique to gliomas but shared across most, if not all, tumor types? Such an extrapolation led to the evaluation of angiogenesis inhibitors in patients with brain tumors, and studies before evaluation

in glioma reported exciting results of bevacizumab in many cancer types. Initial studies in glioma<sup>11,23</sup> were generalized from the colorectal carcinoma literature, in which bevacizumab (antibody that neutralizes the principal angiogenic protein, VEGF) was used in combination with irinotecan. These earlier promising reports then led to a randomized study comparing bevacizumab combined with irinotecan vs bevacizumab alone that revealed no significant advantage conferred by irinotecan, hence leading to FDA approval in 2009 of single-agent bevacizumab for treatment of recurrent high-grade glioma.<sup>12</sup>

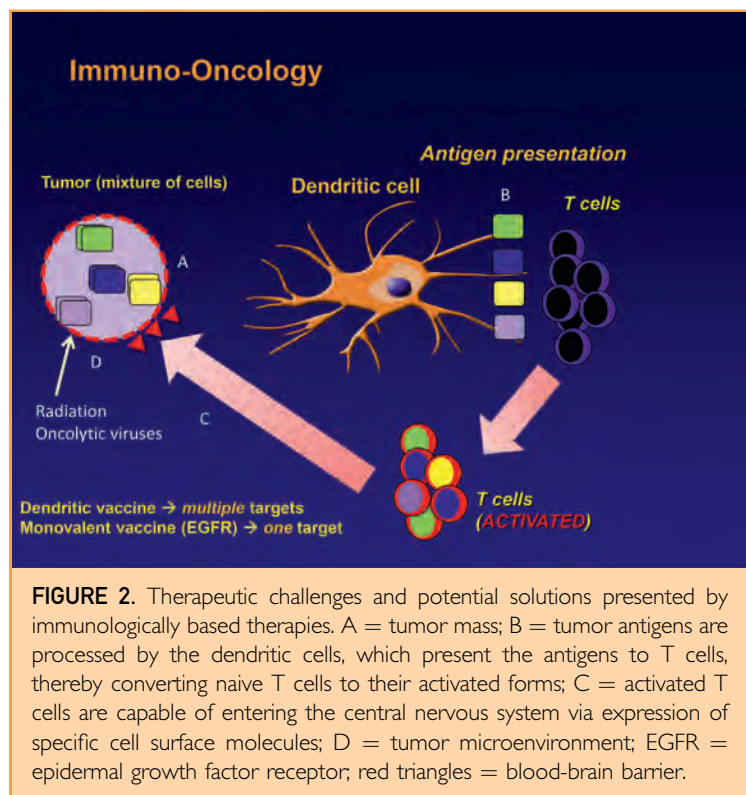
Despite the widespread use of bevacizumab since FDA approval, there still exists no conclusive data that this therapy improves overall survival. In fact, the median time to resistance to bevacizumab is a disappointing 4 months, with tumor cells escaping bevacizumab control due to (1) utilization of alternate angiogenic pathways (eg, platelet-derived growth factor, fibroblast growth factor, mesenchymal stem cells) that are independent of bevacizumab's target VEGF<sup>24</sup> and (2) induction of an evasive phenotype in which tumor cells may take on a more infiltrative/metastatic behavior after exposure to bevacizumab.<sup>25-27</sup>

As a result, many trials have tested other drugs—often the very same small molecule inhibitors that were already known to be ineffective as single agents—and to date, all studies have had negative results. The addition of lomustine, a nitrosourea, to bevacizumab in a phase 2 study increased progression-free and overall survival in the classic subtype of patients with recurrent glioblastoma,<sup>28</sup> and this regimen may show promise in phase 3 studies. Increased understanding of the various angiogenic pathways (especially those not involving VEGF) in glioma growth will then hopefully lead to ways by which we can overcome resistance to current angiogenesis inhibitors.

#### **LEARNING FROM THE PAST: OLDER STUDIES BEARING FRUIT DECADES LATER**

Thus far, we have reviewed promising clinical trial data in high-grade gliomas arising from studies initiated in the early 2000s or later. Similarly, results from studies initiated in the 1990s that have only recently matured have made a huge impact in the care of





patients with low- and intermediate-grade gliomas. Two groups asked the same question: Does chemotherapy add benefit to RT in patients with intermediate- and low-grade glioma? Both studies yielded positive results with a doubling of life expectancy and, moreover, led to further underscoring the importance of molecular markers in treatment planning.

### Intermediate-Grade Glioma

The Radiation Therapy Oncology Group (RTOG) 9402 study, hence named because it was initiated in 1994, evaluated the 3-drug regimen consisting of procarbazine, lomustine [CCNU], and vincristine (PCV) in addition to RT in the treatment of patients with World Health Organization (WHO) grade III/anaplastic oligodendroglial tumors. When initial results were reported in 2006,<sup>29</sup> concurrently with results of a similar study done in Europe by the EORTC,<sup>30</sup> both studies found no difference between the treatment arms. When the data matured 6 years later, the survival curves split specifically for

the patients whose tumors harbored a deletion of chromosome segments 1p and 19q (termed *1p/19q codeletion*). Both studies reported essentially the same findings—the addition of chemotherapy doubled survival from approximately 8 years (RT alone) to 15 years or longer.<sup>31,32</sup> In the absence of *1p/19q codeletion*, the presence of a mutation in the isocitrate dehydrogenase gene (*IDH*) was also predictive of survival benefit from PCV therapy.<sup>33</sup> Both genetic alterations (*1p/19q codeletion* and *IDH* mutations) were not identified until well after these studies had been initiated, but thanks to the foresight of the RTOG and EORTC study teams, archival tumor tissue from study participants could be located and assessed for these key genetic determinants, which yielded practice-altering results guided by molecular variables.

### Low-Grade Glioma

As indicated by its name, the RTOG 9802 study was initiated in 1998. This study, like the one described previously, evaluated the role of adding PCV chemotherapy to RT but this time in the context of low-grade (WHO grade II) gliomas of both oligodendroglial and astrocytic cell types.<sup>34</sup> For patients in the higher-risk category (any patient >40 years of age or any patient regardless of age who had residual tumor after biopsy/surgery), chemotherapy improved overall survival. But similar to the study with grade III oligodendrogliomas, the oligodendroglial tumors as well as tumors harboring the *IDH* mutation derived the most apparent benefit from the chemotherapy. The relatively small number of patients whose tumors were available for *1p/19q* analysis made it difficult to determine if that gene alteration was predictive of chemotherapy benefit.

As such, both the intermediate- and low-grade glioma studies discussed herein determined that the oligodendroglial cell type as well as the presence of *IDH* mutation portends a better outcome with chemotherapy. The experience of these pivotal studies of low- and intermediate-grade glioma is somewhat ironic in that advances in tumor genetics led to a rekindled interest in a chemotherapy regimen (PCV) that was believed to be a thing of the past. Controversy remains regarding



**TABLE 3. Immunotherapeutic Approaches to Address Challenges in Brain Tumor Treatment in Immunological Therapies**

Challenge to treatment	Possible solution/approach
<p>Tumor heterogeneity</p> <p>In “A” on <a href="#">Figure 2</a>, heterogeneity is illustrated by different colored cells (each cell representing a distinct set of molecular alterations and antigens)</p>	<p>Dendritic cell vaccine</p> <p>Antigen-presenting cells or dendritic cells process and present innumerable tumor antigens to T cells to generate activated antitumor T cells</p> <p>Resected tumor serves as a rich source of numerous tumor antigens to be targeted by T cells, thereby addressing the issue of tumor heterogeneity</p>
<p>Antigen presentation by dendritic cells (“B” on <a href="#">Figure 2</a>) is dampened by cell-cell interactions between dendritic cells and T cells. This dampening of antigen presentation serves as a checkpoint to suppress T-cell activation</p>	<p>Checkpoint inhibitor</p> <p>Monoclonal antibodies to disrupt the immunosuppressive cell-cell signaling (example: ipilimumab, a checkpoint inhibitor)</p>
<p>Blood-brain barrier hindering entry of drugs into brain and tumor (“C” on <a href="#">Figure 2</a>)</p>	<p>Activated T cells are capable of entering the central nervous system via expression of specific cell surface molecules</p>
<p>Immunosuppressive factors in tumor microenvironment (“D” on <a href="#">Figure 2</a>)</p> <p>PD-L1 expressed by tumor cells (red triangles on <a href="#">Figure 2</a>) bind to PD-1 receptor on approaching T cells, inducing apoptotic death of T cells</p>	<p>Checkpoint inhibitor</p> <p>Monoclonal antibodies to disrupt interaction between PD-L1 and PD-1 (example: nivolumab)</p>
<p>Immunosuppression by tumor</p> <p>Effectively cloaks tumor cells to avoid detection by T cells and antigen-presenting cells</p>	<p>Dendritic cell vaccine. Patient’s dendritic cells are exposed to tumor antigens extracted from resected tumor to drive T-cell activation</p> <p>Radiotherapy, oncolytic viruses kill a portion of tumor → tumor cell death releases tumor antigens that then drive antigen presentation → recruitment of activated T cells to area of radiotherapy or oncolytic virus injection to augment tumor kill</p>

whether PCV is superior to TMZ in this setting. Perhaps there is no such thing as “old drugs,” but rather simply drugs that have yet to be matched to the appropriate patient population.

#### **A DECADE OF ADVANCES IN GENETICS AND CHEMOTHERAPY: IS IMMUNO-ONCOLOGY THE NEXT FRONTIER?**

The past decade has indeed been eventful, marked by a number of important clinical advances. We can improve survival in low-, intermediate-, and high-grade gliomas by adding chemotherapy to RT, and now for all 3 conditions, the combined therapy is the new standard of care. In all 3 grades of glioma, specific genetic alterations serve as not only prognostic but also predictive markers because they identify which patient population would best benefit from

chemotherapy. However, although the overall life expectancy has increased substantially, treatment resistance is too often an occurrence, largely stemming from 2 major hindrances to therapy—tumor heterogeneity and barriers to drug delivery.

Although a schematic of a single tumor cell as depicted in [Figure 1](#) may be accurate for that one individual tumor cell, the reality is that a patient’s tumor mass is composed of millions of cells, each cell with its potential to diverge and evolve its own molecular alterations, thereby generating extensive intratumoral heterogeneity. In such a system in which, for example, EGFRvIII alteration can be seen in one area of the tumor but not in another, the possible permutations of this and other genetic alterations from one cell to another in a large tumor mass can be endless.<sup>35</sup> Herein lies the challenge of finding a curative treatment—how



**TABLE 4. Molecular/Genetic Markers in Glioma and Their Clinical Relevance—a Road Map for Future Advances in Treatment**

Molecular alteration in glioma	Clinical relevance
<i>MGMT</i> promoter methylation	Sensitivity to alkylator chemotherapy (eg, TMZ)
<i>TERT</i> mutation	Negative prognostic marker when present alone <sup>36,37</sup> ; however, the prognostic/predictive <b>benefit</b> of <i>MGMT</i> methylation may require <i>TERT</i> mutation
1p/19q Codeletion	Positive prognostic marker. Identifies subgroup of gliomas responsive to alkylator-based chemotherapy as well as RT
<i>IDH</i> mutation	Positive prognostic marker. Identifies subgroup of patients with 1p/19q nondeleted oligodendroglioma who may benefit from alkylator chemotherapy
1p/19q Codeletion + <i>IDH</i> mutation + <i>TERT</i> mutation	This combination identifies one of the best prognostic categories for glioma patients
Proneural gene expression profile	Identifies subgroup of patients with GBM who may benefit from bevacizumab added to RT-TMZ
<i>EGFR</i> variant 3 ( <i>EGFRvIII</i> )	Identifies subgroup that may benefit from <i>EGFRvIII</i> -directed vaccine therapies <sup>38</sup>
PD-L1	Activated T cells express PD-1; when PD-L1 (expressed by tumor cells) binds to its receptor PD-1 on T cells, these T cells undergo apoptotic death (hence, mechanism of immune evasion). Target for nivolumab (PD-L1 inhibitor) <sup>39</sup>
CD155	Receptor for infection by oncolytic poliovirus <sup>40</sup>
CD46	Receptor for infection by oncolytic measles virus <sup>41</sup>
Overactive Ras	Permits replication of modified oncolytic reovirus <sup>42</sup>
EGFR = epidermal growth factor receptor; GBM = glioblastoma multiforme; <i>IDH</i> = isocitrate dehydrogenase gene; <i>MGMT</i> = O <sup>6</sup> -methylguanine-DNA methyltransferase gene; RT = radiotherapy; <i>TERT</i> = telomerase reverse transcriptase gene; TMZ = temozolomide.	

to treat such an incredible diversity of tumor cells with just 1, 2, or 3 drugs. The future may lie in immunologic therapies.

Figure 2 and Table 3 illustrate the therapeutic challenges as well as potential solutions presented by immunologically based therapies. The tumor mass (“A” in Figure 2) presents the challenge of the tremendous heterogeneity of cells, each cell harboring antigens distinct from other cells within the mass. These tumor antigens are processed by the dendritic cells, which present the antigens to T cells (“B” in Figure 2), thereby converting naive T cells to their activated forms. There are several checkpoints in this pathway whose function is to dampen T-cell activation in order to avoid an overzealous immune reaction that could lead to autoimmune conditions. Such immunosuppressive checkpoints exist at the point of antigen presentation (interaction between dendritic cell and naive T cells; “B” in Figure 2) and in the tumor microenvironment (“D” in Figure 2) and are

amenable to therapy with checkpoint inhibitors (Table 3).

#### THE MOLECULAR ERA OF NEURO-ONCOLOGY: UPDATED MAP FOR FUTURE ADVANCES

Undoubtedly, the past decade has been a remarkable one, with many advances in treatment options. In regard to chemotherapy, our field has gone from having no clear role for chemotherapy in the treatment of glioma to chemotherapy being able to as much as double life expectancy in the case of low- and intermediate-grade gliomas. Moreover, not only prognosis but also treatment choices can be guided by the tumor’s molecular/genetic alterations as summarized in Table 4.

With the ever-growing importance of genetic alterations to determine prognosis and treatment choices, the diagnostic labels that we ascribe to tumors is shifting from the standard WHO grades II, III, and IV to one of molecularly based diagnoses. This transition



toward molecular classification of gliomas has been evolving over the past 10 to 15 years and reached a tipping point in 2015 when 3 groups (Mayo Clinic/University of California, San Francisco,<sup>36</sup> the Cancer Genome Atlas Network (TCGA) group,<sup>37</sup> and the Japanese group led by Suzuki et al<sup>35</sup>) concurrently published their findings that converged on the same conclusion: that molecularly based diagnosis is superior to diagnosis based on conventional histologic and morphological features of tumor cells. For example, although we would typically expect the prognosis to be grade dependent, exceptions to this general rule are often encountered—eg, a patient with a grade IV/high-grade tumor may have a much longer life expectancy than one who has a grade III/intermediate-grade or even grade II/low-grade tumor. Furthermore, there can be considerable variability in histology-based diagnosis among neuropathologists because of the relatively subjective nature of interpreting cell morphology, nuclear atypia, number of mitotic figures, and other morphological characteristics that determine tumor type and grade. This issue is in contrast to the more binary nature of interpreting genetic tests—for example, 1p/19q alleles are either codeleted or they are not. Along these lines, the aforementioned 3 articles published in 2015 reveal that patients with brain tumors can be grouped into diagnostic clusters based on genetic alterations in which a tumor harboring triple positivity (1p/19q deletion, *IDH* mutation, *TERT* [telomerase reverse transcriptase gene]/telomerase mutation) presents one of the best prognostic groups. Conversely, a tumor harboring none of the alterations portends a prognosis similar to grade IV astrocytoma (glioblastoma) even if the histology may be grade II or III. As such, the 2016 WHO classification of central nervous system tumors has been extensively revised to incorporate genetic alterations.<sup>43</sup> This more accurate classification scheme will also influence future clinical studies, in which eligibility for a specific clinical study will be based more on molecular genetic alterations.

## CONCLUSION

The shift of the neuro-oncology field toward individualized medicine represents a molecular revolution built on a steadfast evolution

and accumulation of many years of rigorous basic and translational research. The past decade that has seen tremendous advances in treatments that prolong life for patients with brain tumors was the product of many preceding years of research. As we look ahead, we rely on the exponential increase in our understanding of glioma biology to serve as fuel for an even better future for our patients. If the numerous scientific advances listed in Table 4 serve in any way as an indicator of what lies ahead, then we can be optimistic.

**Abbreviations and Acronyms:** EORTC = European Organisation for Research and Treatment of Cancer; FDA = Food and Drug Administration; GBM = glioblastoma multiforme; GFR = growth factor receptor; *IDH* = isocitrate dehydrogenase gene; KPS = Karnofsky Performance Status; *MGMT* = O<sup>6</sup>-methylguanine-DNA methyltransferase gene; PCV = procarbazine, lomustine [CCNU], and vincristine; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; TMZ = temozolomide; TTF = tumor-treating field; VEGF = vascular endothelial growth factor; WHO = World Health Organization

**Potential Competing Interests:** Dr Uhm has received honoraria from Novocure, manufacturer of the Optune tumor-treating field device that is discussed in this article.

**Correspondence:** Address to Joon H. Uhm, MD, Department of Neurology and Division of Neuro-Oncology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (uhm.joon@mayo.edu). Individual reprints of this article and a bound reprint of the entire Symposium on Neurosciences will be available for purchase from our website [www.mayoclinicproceedings.org](http://www.mayoclinicproceedings.org).

**The Symposium on Neurosciences will continue in an upcoming issue.**

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# **Delayed response and survival from NovoTTF-100A in recurrent GBM**

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## Delayed response and survival from NovoTTF-100A in recurrent GBM

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**Abstract** We present a 48-year-old male with recurrent glioblastoma (GBM) who was enrolled in the NovoTTF-100A landmark phase III study and has been on device for >6 years. During this time, his magnetic resonance images demonstrated initial growth followed by a slow decrease in enhancement with continued residual disease. Long-term survivors in patients with recurrent GBM are rare, especially in the absence of definitive local treatment such as surgery or radiosurgery. We present the clinical, imaging and pathological findings for this patient in relation to use of the NovoTTF-100A device.

**Keywords** Glioblastoma · Brain tumor · Tumor treatment fields · Recurrent tumor · Survival

### Introduction

Patients with recurrent glioblastoma (GBM) have poor outcomes with median survival of <6 months in most series [1]. Reports of patients having prolonged survival with GBM are limited mainly to treatments for primary disease [2–5]. With patients living longer, more investigations are being conducted in second line treatment [1]. The recent phase II (BRAIN) study demonstrated median survival of 9 months with bevacizumab-based treatment [1].

NovoTTF-100A is a recently FDA-approved device that creates electrical fields within the tumor that disrupt cell division during anaphase [6]. Patients wear non-invasive transducer arrays on their scalp during most of the day. A landmark phase III trial in recurrent GBM demonstrated the device has equivalent therapeutic benefit to chemotherapy, with less toxicity and with improved quality of life measures [6].

We report a patient enrolled in this trial that has continued to respond to the NovoTTF-100A device for more than 6 years, representing one of the longest reported survivors of recurrent GBM.

### Case report

A 48-year-old Hispanic male presented in February 2004 with a generalized tonic-clonic seizure. MRI of the brain demonstrated an enhancing mass in the right parietal lobe. He initially underwent debulking of the mass, and final

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pathology was interpreted as suggestive of infiltrating glioma. Postoperatively, he developed noticeable, 4/5, left hemiparesis with left facial droop. Without a conclusive diagnosis, he was recommended a repeat craniotomy, which he declined (Figs. 1, 2).

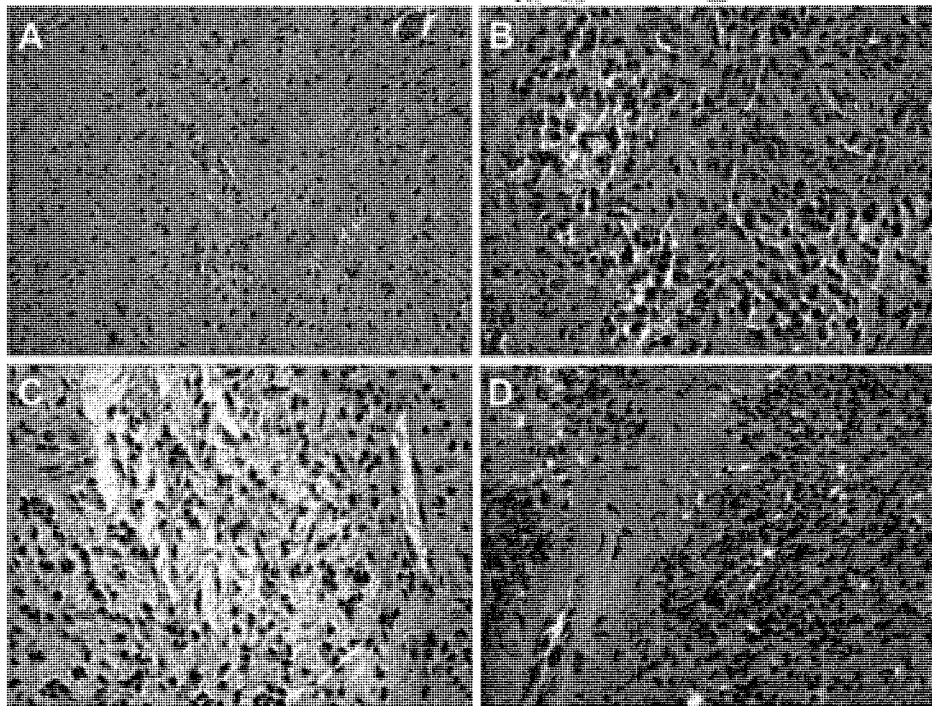
Nine months later, based on imaging studies he underwent a second right frontoparietal craniotomy and biopsy with debulking of the mass. He received impregnated carmustine wafers during surgery. Pathological analysis demonstrated GBM having brisk mitotic activity, widespread microvascular proliferation, pseudopalisading necrosis with significant nuclear pleomorphism and atypia. It also had oligodendroglial features, and chromosomal analysis revealed heterozygous deletions of both 1p and 19q chromosomes [7]. Methylation analysis for the promoter region of the *MGMT* gene demonstrated positive methylation.

He was treated with the involved-field cranial irradiation and concomitant daily temozolomide, which he tolerated well. Although he had a delay in starting the maintenance portion, imaging studies following his eleventh cycle demonstrated progression of his enhancing lesion. Almost 2 years after his initial tumor resection, he underwent a

third craniotomy for surgical debulking, which demonstrated similar pathology as his second surgery. Five months later, he received radiation boost via Gamma Knife as he showed increased enhancement. Imaging performed 4 months after this procedure revealed progression. He was then enrolled in the Novocure phase III recurrent trial, and on November 15, 2006, he began treatment with the NovoTTF-100A device for 22 h daily. Since starting this treatment, he has been clinically stable. During the initial MRI scans on study, his enhancing lesion grew in size, but did not meet criteria for disease progression, and therefore, he remained in the trial. This was then followed by a period of slow but continued decrease in enhancement that has since stabilized. He remains active and functional and continues using the device.

## Discussion

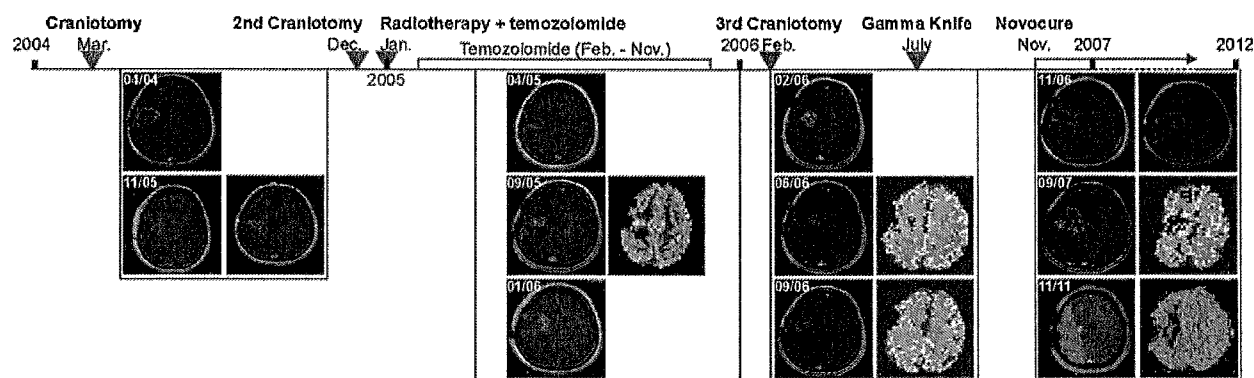
The NovoTTF-100A device is a portable battery-operated device that generates alternating electric fields called tumor treating fields (TTFields). Charged intracellular dipoles such as microtubules are required for cell division and are



**Fig. 1** **a** Hematoxylin and eosin-stained section of brain biopsy specimen from 4/2004 with mildly increased cellularity and glial atypia suggestive of infiltrating glioma (magnification:  $\times 200$ ). **b** Hematoxylin and eosin-stained section of GBM from 11/2004 with increased cellularity, significant glial atypia and pleomorphism, mitotic activity and microvascular proliferation (magnification:  $\times 400$ ). **c** Hematoxylin and eosin-stained section of GBM from

11/2004. Some tumor areas were dominated by tumor cells featuring round nuclei consistent with an oligodendroglioma component (magnification:  $\times 400$ ). **d** Hematoxylin and eosin-stained section of resection specimen from 2/2006 with highly cellular glioma and vascular changes consistent with radiation-related changes (magnification:  $\times 400$ )





**Fig. 2** Results of diagnostic MRI throughout disease course. T1-weighted MRI of the brain with Gadolinium contrast-axial section with accompanied perfusion study at similar structural level. These images corresponds to the timeline-demonstrating therapy and disease activity. In the perfusion study, voxels that are red correspond to high

blood flow, as seen with the outer cerebral vasculature and growing tumor. Blue colored voxels correspond to areas of low blood flow, as seen in white matter, with gradation of blood flow visualized by changes in the red-to-blue color spectrum. Note that most recent image does not demonstrate increased perfusion

disrupted by TTFields. This disruption leads to an arrest on cell proliferation with subsequent apoptosis and theoretically provides cytotoxic therapy [6]. The prolonged survival in our patient receiving only TTFields is consistent with these pre-clinical findings.

Our patient's diagnosis of GBM was confirmed by having two independent neuro-pathologic reviews. Histologically, the hallmarks of GBM were present: widespread microvascular proliferation and pseudopalisading necrosis. However, he does have the subclass of GBM-containing oligodendroglial component [7]. Although debated, this is associated with improved outcomes. Our patient's clinical course was progressive, requiring multiple craniotomies, chemotherapy and radiation.

Radiation necrosis also needs be considered. Radiation damage to vascular endothelial cells can result in compromise of the blood-brain barrier. Although radiation necrosis cannot be ruled out, the enhancing lesion on MRI demonstrated increased cerebral blood volume on perfusion studies, which is consistent with recurrent tumor. Also, the resected samples in the two craniotomies following his initial treatment retained active tumor cells. It is notable that patients with methylated *MGMT* gene have increased risk of developing pseudoprogression; however, he started TTF therapy nearly 2 years from receiving his concurrent radiation and temozolomide. Finally, radiation necrosis or pseudoprogression will in time generally have a self-limiting course, although many cases will have disease progression as viable tumor frequently coexists within areas of radiation necrosis, and our patient has been on device for greater than 6 years with imaging evidence of residual enhancement [8]. This leads us to conclude that the imaging findings represent disease progression.

In conclusion, our patient is a unique long-term survivor of GBM with evidence of residual disease. He has received

significant amount of treatment, but currently for >6 years is only receiving the NovoTTF-100A device.

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**Conflict of interest** None.

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The NovoTTF-100A System is approved for the treatment of patients with recurrent GBM. Please refer to the IFU for full prescribing information.

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**Keywords:** dexamethasone; glioblastoma; NovoTTF-100A; tumour immunology; chemotherapy

# Dexamethasone exerts profound immunologic interference on treatment efficacy for recurrent glioblastoma

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**Background:** Patients with recurrent glioblastoma have a poor outcome. Data from the phase III registration trial comparing tumour-treating alternating electric fields (TTFields) vs chemotherapy provided a unique opportunity to study dexamethasone effects on patient outcome unencumbered by the confounding immune and myeloablative side effects of chemotherapy.

**Methods:** Using an unsupervised binary partitioning algorithm, we segregated both cohorts of the trial based on the dexamethasone dose that yielded the greatest statistical difference in overall survival (OS). The results were validated in a separate cohort treated in a single institution with TTFields and their T lymphocytes were correlated with OS.

**Results:** Patients who used dexamethasone doses  $>4.1$  mg per day had a significant reduction in OS when compared with those who used  $\leq 4.1$  mg per day, 4.8 vs 11.0 months respectively ( $\chi^2 = 34.6$ ,  $P < 0.0001$ ) in the TTField-treated cohort and 6.0 vs 8.9 months respectively ( $\chi^2 = 10.0$ ,  $P < 0.0015$ ) in the chemotherapy-treated cohort. In a single institution validation cohort treated with TTFields, the median OS of patients who used dexamethasone  $>4.1$  mg per day was 3.2 months compared with those who used  $\leq 4.1$  mg per day was 8.7 months ( $\chi^2 = 11.1$ ,  $P = 0.0009$ ). There was a significant correlation between OS and T-lymphocyte counts.

**Conclusions:** Dexamethasone exerted profound effects on both TTFields and chemotherapy efficacy resulting in lower patient OS. Therefore, global immunosuppression by dexamethasone likely interferes with immune functions that are necessary for the treatment of glioblastoma.

Patients with recurrent glioblastoma have limited treatment options. Bevacizumab is a standard of care for patients with recurrent glioblastoma and it produces an objective response rate of 25–60% (Wong *et al*, 2011). However, its ability to prolong patient overall survival (OS) is questionable (Iwamoto and Fine, 2010; Reardon *et al*, 2012). The NovoTTF-100A device is another FDA-approved treatment for recurrent glioblastoma that works by emitting tumour-treating alternating electric fields (TTFields) via two pairs of transducer arrays placed orthogonally on the scalp and acts to perturb tumour cells during mitosis (Kirson *et al*, 2004, 2007; Gera *et al*, 2015). Preclinical data show that cells affected by TTFields exhibit violent plasma membrane blebbing that disrupts the normal spatial ordering of the mitotic chromosomes.

This results in asymmetric chromosome segregation and aneuploidy owing to defects in cytokinesis and aberrant mitotic exit. Furthermore, these cells also exhibit signs of stress that include elevated cell surface expression of calreticulin, which makes them more readily detectable by phagocytic immune cells, facilitating an immune response against the tumour (Lee *et al*, 2013). Importantly, the NovoTTF-100A device was demonstrated to possess equivalent efficacy when compared with best physician's choice (BPC) chemotherapy in the registration phase III clinical trial, but without the myeloablative toxicities associated with systemic chemotherapies that may cause secondary systemic infection or interference with immune effector function (Vecht *et al*, 1994; Hughes *et al*, 2005; Stupp *et al*, 2012; Fonkem and Wong, 2012).

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More recently, a prespecified interim analysis of the results from an upfront phase III clinical trial in newly diagnosed glioblastoma patients, comparing NovoTTF-100A plus adjuvant temozolomide *vs* adjuvant temozolomide alone, revealed significantly improved patient outcome with a respective progression-free survival of 7.1 *vs* 4.0 months and OS of 19.6 *vs* 16.6 months (Stupp *et al*, 2014). Compared with newly diagnosed glioblastomas, patients with recurrent glioblastoma likely have several factors that led to a worse outcome, including clonal evolution of the tumour, evasion of the immune system and reduction of immune competence because of prior exposure to chemotherapy.

Dexamethasone is commonly used to treat neurologic symptoms caused by the glioblastoma (Vecht *et al*, 1994). However, it also has a plethora of systemic toxicities, including gastrointestinal haemorrhage with or without perforation, infection, and hyperglycaemia (Heimdal *et al*, 1992). Although dexamethasone has not been shown to interfere directly with the efficacy of treatments against glioblastoma, there is emerging evidence from both preclinical and clinical data in other malignancies to suggest that dexamethasone may affect the patient's antitumour immunity. First, although the immune system has evolved multiple mechanisms to recognise and eliminate neoplastic cells (Senovilla *et al*, 2013), tumours emerge within the patient when they escape immune surveillance (Mittal *et al*, 2014). At this point, the tumour further subverts the immune system by eliciting normal wound healing and tissue remodelling responses, whereas promoting a state of immune privilege within the tumour microenvironment (Schreiber *et al*, 2011). In this setting, dexamethasone may potentiate existing local immunosuppression via global induction of  $\text{I}\kappa\text{B}\alpha$  and inhibition of NF- $\kappa\text{B}$  activity in lymphocytes, resulting in global immunosuppression (Auphan *et al*, 1995). Second, dexamethasone can lower the number of  $\text{CD4}^+$  lymphocytes in newly diagnosed patients with glioblastoma treated with radiation alone or in combination with temozolomide, and this attenuated  $\text{CD4}^+$  lymphocyte count is associated with increased infections and decreased survival (Hughes *et al*, 2005; Grossman *et al*, 2011). Lastly, recent clinical trial data have shown that there were more systemic and central nervous system responders to ipilimumab, an immune checkpoint inhibitor, in the cohort taking no dexamethasone as compared with the cohort taking dexamethasone, suggesting that dexamethasone interferes with the efficacy of ipilimumab (Margolin *et al*, 2012).

In this paper, we present evidence that immune suppression by dexamethasone markedly interferes with the clinical efficacy of two disparate therapies for recurrent glioblastoma: electric field-based therapy delivered by the NovoTTF-100A as well as conventional chemotherapies. Unlike prior clinical trials, the cohort treated with TTField monotherapy offered us an opportunity to study unambiguously the effect of dexamethasone on patient survival unencumbered by concurrent chemotherapies that suppress the immune system. We also present data that strongly support a role for immune competence in effecting TTField treatment by analysing T-cell subsets measured in a separate cohort of patients for validation.

## PATIENTS AND METHODS

**Patients.** Subjects signed informed consent from their respective treating institutions before participation in the phase III trial comparing NovoTTF-100A *vs* BPC chemotherapy (Fonkem and Wong, 2012; Stupp *et al*, 2012). A *post hoc* analysis of the dexamethasone effect on the two cohorts was performed based on anonymised data obtained from the sponsor, from whom the corresponding author had full access to the primary data. The outcome of the analysis was then validated retrospectively, under

an institutional review board-approved protocol from Dana Farber/Harvard Cancer Center (protocol no. 12-519), using a separate cohort of patients who were treated with NovoTTF-100A and bevacizumab at Beth Israel Deaconess Medical Center.

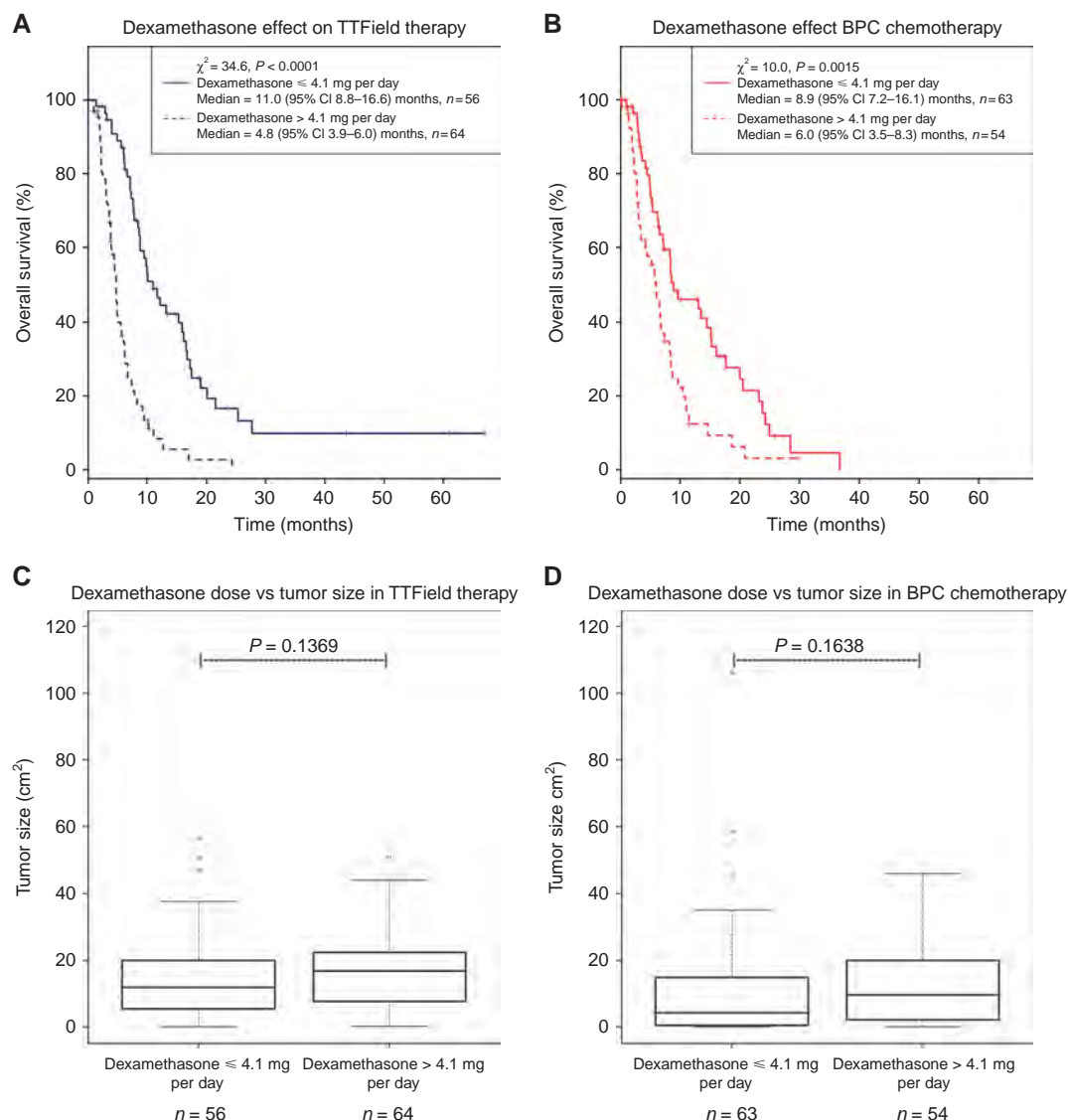
**Statistical analysis.** Statistical analyses were performed by using R statistics base package (<http://www.r-project.org>) and its libraries. Two-tailed Wilcoxon's rank-sum test with continuity correction was used to determine whether two independent groups of data were statistically different from each other. A modified binary search algorithm (Knuth, 1971; Tøndel *et al*, 2002), written in R, was used to iteratively partition data in both two and three dimensions. The Loess local nonparametric polynomial regression was used to perform curve fitting of the OS as a function of dexamethasone dose (Cleveland, 1979; Shipley and Hunt, 1996; Cleveland and Loader, 1996) and OS was analyzed using Kaplan–Meier statistics (Kaplan and Meier, 1958).

## RESULTS

**Effect of dexamethasone on TTField therapy and BPC chemotherapy.** Our previous *post hoc* analysis of responders in the phase III trial demonstrated that responders to TTField therapy required significantly lower doses of dexamethasone compared with non-responders (Wong *et al*, 2014). We therefore investigated further whether there was a threshold dose of dexamethasone that affected outcome within the entire trial population. Using an unsupervised binary partitioning algorithm (Knuth, 1971; Tøndel *et al*, 2002), we stratified the TTField therapy cohort based on the dexamethasone dose that yielded the greatest statistical difference in median OS. The results revealed that subjects who used  $>4.1$  mg per day dexamethasone ( $n=64$ ) exhibited a significantly shortened median OS of 4.8 months (95% confidence interval (CI): 3.9–6.0) *vs* those who used  $\leq 4.1$  mg per day ( $n=56$ ), with a median OS of 11.0 months (95% CI: 8.8–16.6) ( $\chi^2=34.6$ ,  $P<0.0001$ ; Figure 1A). We then used the same dexamethasone cutoff to stratify control patients in the BPC chemotherapy cohort and observed a similar, albeit less robust, dichotomisation, with a respective median OS of 6.0 months (95% CI: 3.5–8.3) ( $n=54$ ) *vs* 8.9 months (95% CI: 7.2–16.1) ( $n=63$ ) ( $\chi^2=10.0$ ,  $P=0.0015$ ; Figure 1B) for those receiving  $>4.1$  *vs*  $\leq 4.1$  mg per day of dexamethasone, respectively. There are two potential explanations for these results: either patients with larger, more aggressive tumours required a higher dose of dexamethasone for symptom control or doses of dexamethasone  $>4.1$  mg per day interfered with both therapeutic interventions used in this trial. However, tumour size did not differ statistically between patient cohorts that used dexamethasone at either  $>4.1$  or  $\leq 4.1$  mg per day (Figures 1C and D). Therefore, factors other than tumour size influence the OS of subjects receiving high *vs* low doses of dexamethasone.

To further investigate the effect of dexamethasone on patient outcome, we compared the survival characteristics of the cohort treated with TTField therapy to the one treated with BPC chemotherapy in the respective dexamethasone dosage groups. First, we compared the two treatment groups when the dosage of dexamethasone used was  $\leq 4.1$  mg per day. Although the two OS curves overlapped ( $\chi^2=0.9$ ,  $P=0.3510$ ; Figure 2A), we detected a marked separation between these two curves at time points less than the median OS. Indeed, when we compared the survival curves of the two cohorts for subjects who used dexamethasone  $\leq 4.1$  mg per day and possessed survival times of less than the median OS, we found a significant difference between the two subgroups, with a median OS of 6.6 (range 1.4–10.1) months for the TTField-treated subgroup ( $n=31$ ) *vs* 3.9 (range 0.0–8.6) months for the BPC chemotherapy-treated subgroup ( $n=40$ ) ( $P=0.0015$ ; Figure 2C). However, for subjects who lived longer





**Figure 1.** Kaplan–Meier OS and tumour size with respect to dexamethasone requirement of  $\leq 4.1$  vs  $> 4.1$  mg per day from subjects enrolled in the phase III trial comparing TTField therapy vs BPC chemotherapy. **(A)** Subjects enrolled in the TTField treatment arm taking dexamethasone  $\leq 4.1$  (solid blue) vs  $> 4.1$  (dashed blue) mg per day, which was determined by an unsupervised binary partitioning algorithm. Subjects who used  $\leq 4.1$  mg per day of dexamethasone ( $n = 56$ ) had a median OS of 11.0 months (95% CI: 8.8–16.6) as compared with those who used  $> 4.1$  mg per day ( $n = 64$ ) had a median OS of 4.8 months (95% CI: 3.9–6.0) ( $\chi^2 = 34.6, P < 0.0001$ ). **(B)** Subjects enrolled in the BPC chemotherapy arm taking dexamethasone  $\leq 4.1$  (solid red) vs  $> 4.1$  (dashed red) mg per day was determined by the same unsupervised binary partitioning algorithm. Subjects who used  $\leq 4.1$  mg per day of dexamethasone ( $n = 63$ ) had a median OS of 8.9 months (95% CI: 7.2–16.1) as compared with those who used  $> 4.1$  mg per day ( $n = 54$ ) had a median OS of 6.0 months (95% CI: 3.5–8.3) ( $\chi^2 = 10.0, P = 0.0015$ ). **(C)** Box-and-whisker plot of bidimensional tumour size in the TTField therapy cohort that received dexamethasone  $\leq 4.1$  vs  $> 4.1$  mg per day. Subjects who took dexamethasone  $\leq 4.1$  mg per day ( $n = 56$ ) had a median tumour size of 11.9 (range 0.0–56.7)  $\text{cm}^2$  as compared with those who used  $> 4.1$  mg per day ( $n = 64$ ) had a median tumour size of 16.8 (range 0.3–51.0)  $\text{cm}^2$  ( $P = 0.1369$ ). **(D)** Box-and-whisker plot of bidimensional tumour size in the BPC chemotherapy cohort that received dexamethasone  $\leq 4.1$  vs  $> 4.1$  mg per day. Subjects who took dexamethasone  $\leq 4.1$  mg per day ( $n = 63$ ) had a median tumour size of 4.2 (range 0.0–11.2)  $\text{cm}^2$  as compared with those who used  $> 4.1$  mg per day ( $n = 54$ ) had a median tumour size of 9.6 (range 0.0–46.0)  $\text{cm}^2$  ( $P = 0.1638$ ).

than the median OS, there was no difference in the OS curves, with a median OS of 16.7 (range 11.0–66.9) months for the TTField-treated subgroup ( $n = 25$ ) vs 16.8 (range 8.9–36.7) months for the BPC chemotherapy-treated subgroup ( $n = 23$ ) ( $P = 0.5773$ ; Figure 2E). In contrast, among subjects who received high dexamethasone doses of  $> 4.1$  mg per day, the overlapping OS curves ( $\chi^2 = 1.5, P = 0.2240$ ; Figure 2B) appeared to diverge for the subjects whose survival were greater than the median OS. Remarkably, the TTField-treated subgroup was worse compared with the BPC chemotherapy-treated subgroup when treated with

dexamethasone doses  $> 4.1$  mg per day, with a respective median OS of 6.7 (range 4.8–24.3) months ( $n = 29$ ) vs 8.7 (range 6.0–29.6) months ( $n = 22$ ) ( $P = 0.0097$ ; Figure 2D). However, for subjects whose survival were less than the median OS and used  $> 4.1$  mg per day dexamethasone, there was no difference between the TTField-treated and the BPC chemotherapy-treated subgroups, with the former having a median OS of 3.0 (range 0.8–4.5) months ( $n = 35$ ) as compared with the latter having a median OS of 2.8 (range 0.2–5.8) months ( $n = 32$ ) ( $P = 0.8456$ ; Figure 2E). Collectively, the data in Figures 2C and D indicate that the extent



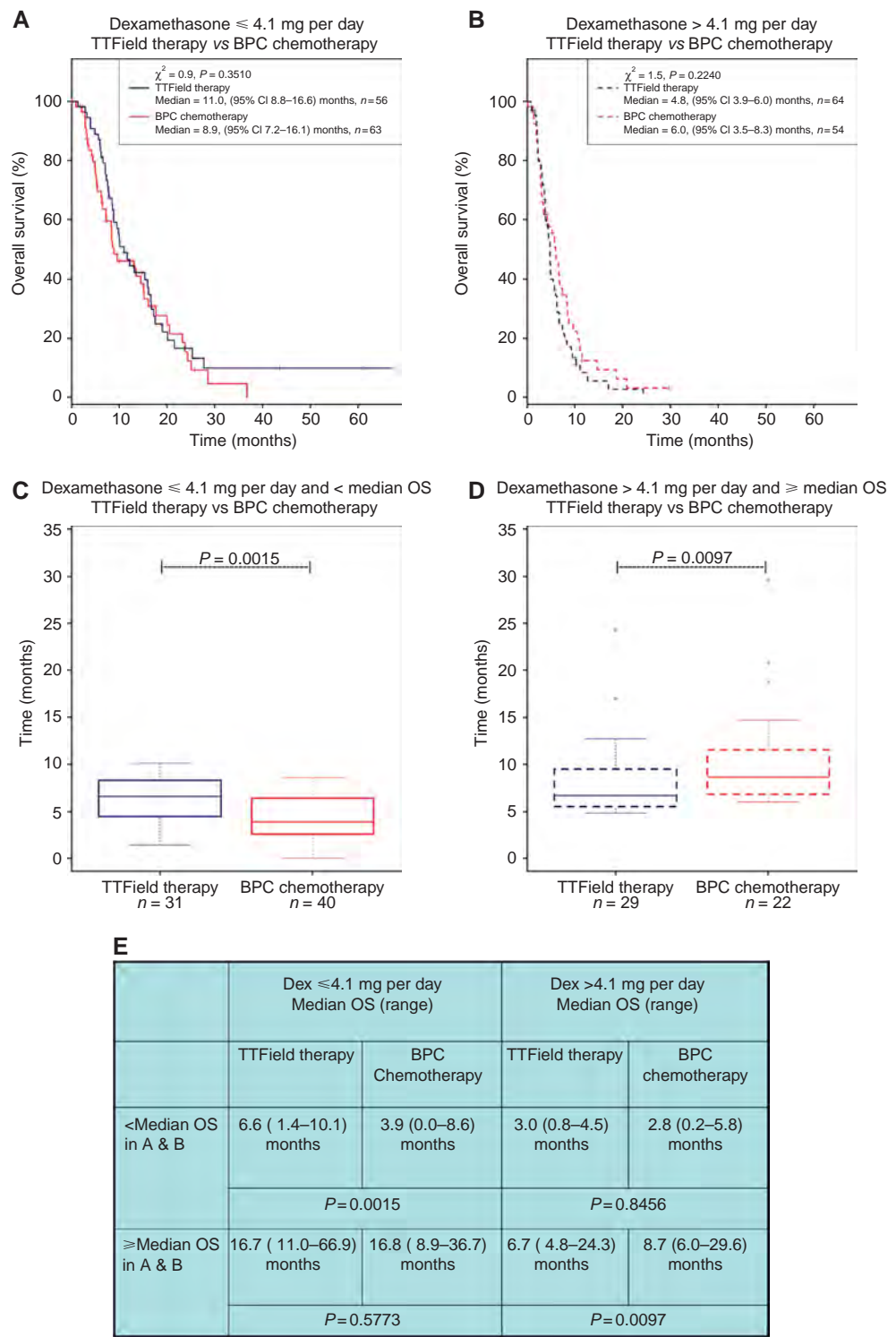


Figure 2. Comparison of OS in subjects treated with TTField therapy vs BPC chemotherapy segregated by dexamethasone usage. (A) Comparison of subjects using dexamethasone  $\leq 4.1$  mg per day in both TTField therapy (blue) and BPC chemotherapy (red) arms. (B) Comparison of subjects using dexamethasone  $> 4.1$  mg per day in both TTField therapy and BPC chemotherapy arms. (C) Box-and-whisker plot of OS between TTField vs BPC chemotherapy-treated subjects using  $\leq 4.1$  mg per day of dexamethasone and  $<$  the median OS in (A). The median OS was 6.6 months (range 1.4–10.1) for TTField-treated subjects ( $n = 31$ ) vs 3.9 months (range 0.0–8.6) for BPC chemotherapy-treated subjects ( $n = 40$ ) ( $P = 0.0015$ ). (D) Box-and-whisker plot of OS between TTFields vs BPC chemotherapy-treated subjects using  $> 4.1$  mg per day of dexamethasone and  $\geq$  the median OS in (B). The median OS was 6.7 months (range 4.8–24.3) for TTField-treated subjects ( $n = 29$ ) vs 8.7 months (range 6.0–29.6) for BPC chemotherapy-treated subjects ( $n = 22$ ) ( $P = 0.0097$ ). (E) Median OS, range, and  $P$ -values for the four subgroups: (i) dexamethasone  $\leq 4.1$  mg per day and  $<$  median OS in (A), (ii) dexamethasone  $> 4.1$  mg per day and  $<$  median OS in (B), (iii) dexamethasone  $\leq 4.1$  mg per day and  $\geq$  median OS in (A), and (iv) dexamethasone  $> 4.1$  mg per day and  $\geq$  median OS in (B).



of dexamethasone exposure not only predicted treatment efficacy but also strongly suggest that TTField therapy is superior to BPC chemotherapy in the setting of low dexamethasone usage. However, under the influence of higher dexamethasone usage, the benefit of TTField therapy appeared to be negated to a greater extent when compared with BPC chemotherapy as if TTField-treated subjects were not provided with any therapy at all.

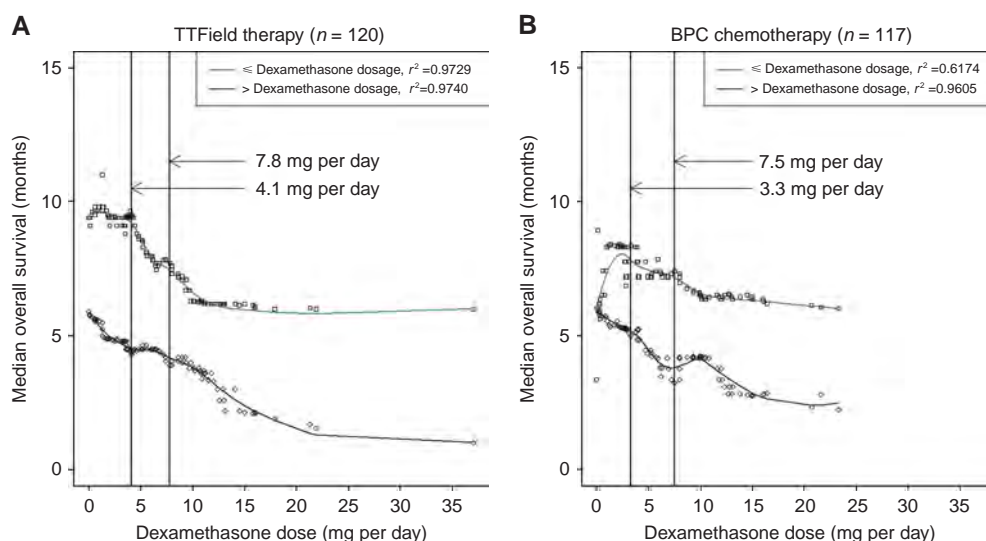
#### Dose-dependent effect of dexamethasone on treatment efficacy.

We next asked whether or not dexamethasone has a dose-dependent influence on treatment efficacy by analysing the entire dose spectrum used in the trial. We partitioned the TTField-treated cohort using a dexamethasone dose cutoff from 0.0 to 37.0 mg per day, plotted the respective median OS of the groups at  $\leq$  cutoff or  $>$  cutoff vs successive dexamethasone dosages, and fitted the data with the best curves using the nonparametric Loess local polynomial regression (Figure 3) (Cleveland, 1979; Cleveland and Loader, 1996; Shipley and Hunt, 1996). In addition, we plotted the log-rank  $P$ -values of the dichotomised groups in each successive dexamethasone dosage and found two nadir  $P$ -values of 0.00000008 and 0.00002524 corresponding to dexamethasone doses of 4.1 and 7.8 mg per day, respectively. We observed that there was decremental OS starting at a dexamethasone dose of 4.1 mg per day and, with successive increases of dexamethasone, reached an inflection point at 7.8 mg per day, after which the rate of OS decreased slowly (Figure 3A).

We also performed the same dose-dependent analysis of dexamethasone in the BPC chemotherapy-treated cohort and found a nadir  $P$ -value of 0.00163291 at 3.3 mg per day and another of 0.00011858 at 7.5 mg per day. Similarly, the best-fit curve derived in Figure 3B also suggests that the dexamethasone dose near 4 mg per day may also represent a point at which decremental OS can be observed with successive increases in dexamethasone dosage. This progressive decrement in OS occurred with successive increases of dexamethasone until an inflection point is observed at a dose near 7.5 mg per day, after which the rate of OS decreased slowly. Taken together, both cohorts experienced interference from dexamethasone at a dose near 4.0 mg per day and a maximal effect was observed near 7.5 mg per day.

**Validation of the dexamethasone effect on TTField-treated patients from a single institution.** We next proceeded to validate the observed dexamethasone effect on patient outcome within the trial by retrospectively analysing our own single-institution cohort. From November 2012 to February 2014, we treated 38 patients (Table 1) using TTField monotherapy as treatment or in combination with bevacizumab, whereas dexamethasone usage was aggressively reduced. Three patients who were referred specifically to our institution did not receive TTField therapy because of patient choice of other treatments, severe medical comorbidities, or advanced intracranial disease that was deemed more suitable for hospice care. Among the remaining 35 patients, their median OS was 4.3 months (95% CI: 3.5–8.7). To properly compare this cohort with the subjects enrolled in the phase III trial, we included only those with a KPS  $\geq$  70 or greater ( $n = 23$ ) in our validation set. This sub-population exhibited a median OS of 8.0 months (95% CI: 3.8–13.8) compared with 3.2 months (95% CI: 1.4–NA) for the remaining patients with a KPS  $<$  70 ( $n = 12$ ) ( $\chi^2 = 8.5$ ,  $P = 0.0035$ ; Figure 4A). We then applied a cutoff of dexamethasone 4.1 mg per day as was found in our previous binary partitioning analysis. Patients who used dexamethasone  $\leq$  4.1 mg per day had a significantly longer OS compared with those who used  $>$  4.1 mg per day, with a median OS of 8.7 months (95% CI: 6.7–NA) ( $n = 19$ ) vs 3.2 months (95% CI: 1.2–NA) ( $n = 4$ ), respectively ( $\chi^2 = 11.1$ ,  $P = 0.0009$ ; Figure 4B). Although our single-institution cohort has fewer patients compared with the cohorts in the phase III trial, we nevertheless observed a robust segregation of OS in the patient groups, validating the previously observed effect of dexamethasone on patient outcome.

Comparison of patients within the validation cohort with a KPS  $\geq$  70 and dexamethasone usage  $\leq$  4.1 mg per day ( $n = 19$ ) to the phase III TTField therapy cohort who used dexamethasone  $\leq$  4.1 mg per day ( $n = 56$ , from Figure 2A) revealed no statistical difference between the two groups, with a median OS of 8.7 months (95% CI: 6.7–NA) vs 11.0 months (95% CI: 8.8–16.6), respectively ( $\chi^2 = 2.1$ ,  $P = 0.1520$ ; Figure 4C). We next asked whether important prognostic factors within our cohort varied relative to patients within the phase III cohort by examining the possible effects of age and tumour size. The median age of our



**Figure 3.** Loess local polynomial regression of median OS vs dexamethasone dose. Dexamethasone was treated as a discrete variable successively and the median OS was plotted for the group  $\leq$  (green) and  $>$  (blue) compared with the variable dosage of dexamethasone. Curve fitting was performed using the Loess local polynomial regression. **(A)** In the TTField therapy cohort ( $n = 120$ ), there was decremental OS from 4.1 mg per day that reached an inflection point at 7.8 mg per day, after which the rate of OS decrease slowed. **(B)** In the BPC chemotherapy cohort ( $n = 117$ ), there was decremental OS from 3.3 mg per day that reached an inflection point at 7.5 mg per day, after which the rate of OS decrease slowed.



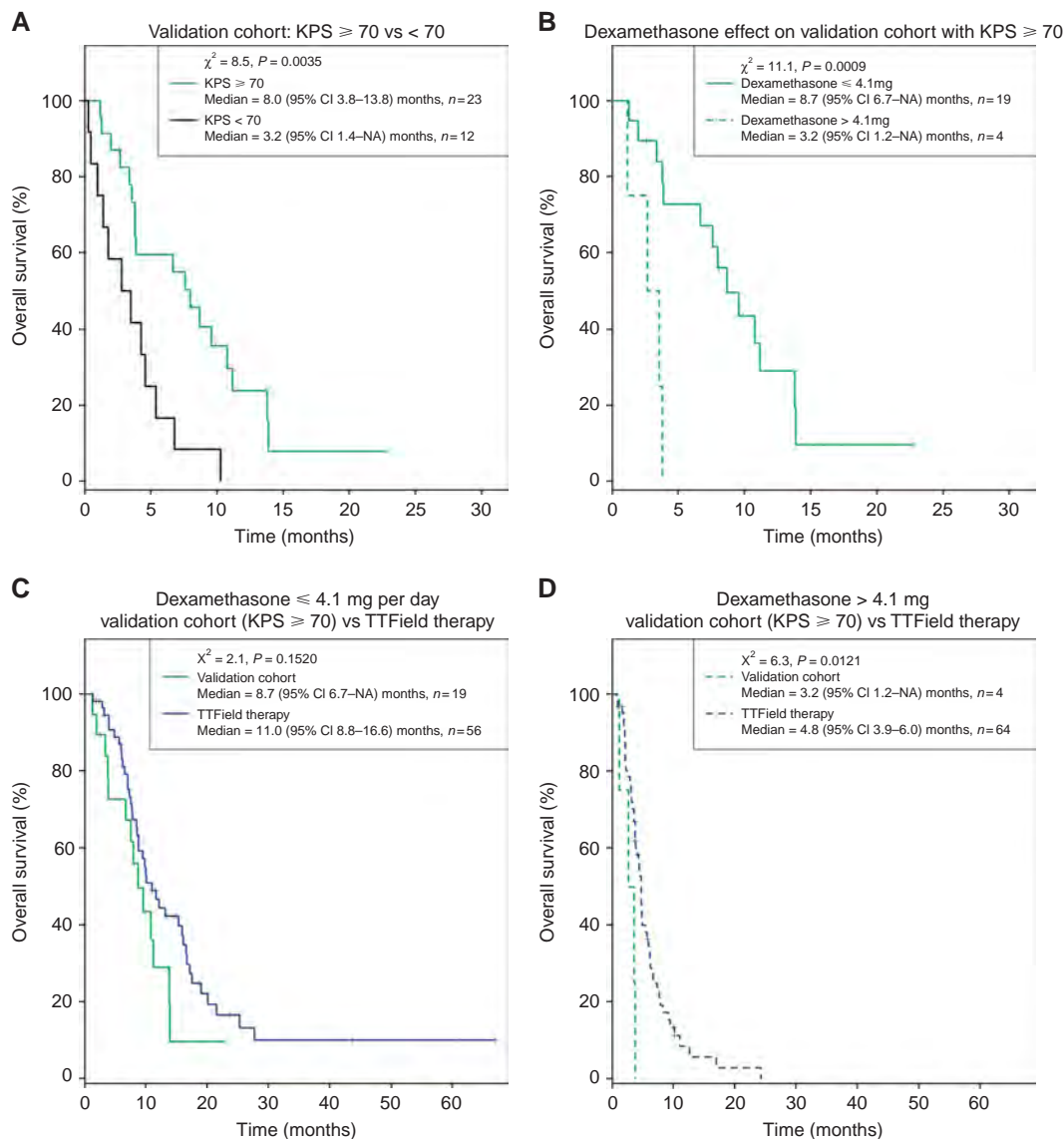
Table 1. Patient characteristics in the validation cohort and the NovoTTF-100A cohort in phase III trial			
Patient characteristics	Validation cohort (n = 35)	NovoTTF-100A cohort (n = 120)	P-value
Age (range)	57 (30 – 77) years	54 (24–80) years	
Gender			
Male	22 (63%)	92 (77%)	
Female	13 (37%)	28 (23%)	
Karnofsky performance status			
Median	70 (range 50–90)	80 (range 50–100)	
Tumour size, bidimensional			
T1 Gad, median (range) (cm <sup>2</sup> )	12.2 (0.3 – 40.6)	14.2 (0.0–56.7)	0.6178
FLAIR, median (range) (cm <sup>2</sup> )	35.2 (7.0 – 90.9)	N/A	
Dexamethasone dose			
Median (range) (mg per day)	3.0 (0.0 – 15.0)	4.7 (0.0–37.5)	
Absolute T-cell subsets			
CD3, median (range) (cells per mm <sup>3</sup> )	733 (70 – 1458)	N/A	
CD4, median (range) (cells per mm <sup>3</sup> )	414 (25 – 788)	N/A	
CD8, median (range) (cells per mm <sup>3</sup> )	302 (44 – 1039)	N/A	
Prior therapy			
First recurrence	6 (17%)	11 (9%)	
Second recurrence	10 (29%)	58 (48%)	
Third recurrence	19 (54%)	51 (43%)	
Prior bevacizumab	25 (71%)	23 (19%)	
Outcome			
Overall survival, median (months)	4.3 (95% CI: 3.5–8.7)	7.1 (95% CI: 6.1–8.8)	0.0468
Abbreviations: CI = confidence interval; FLAIR = fluid-attenuated inversion recovery; Gad = gadolinium; N/A = not applicable; TTF = tumour-treating alternating electric field.			

cohort was 57 (range 30–77) years and it is not different from the median age of 54 (range 24–80) years in the TTField-treated cohort from the phase III trial (Stupp *et al*, 2012). Average tumour size in our cohort as measured by gadolinium-enhanced T1-weighted MRI showed a median bidimensional measurement of 12.2 (range 0.30–40.6) cm<sup>2</sup>, which is similar to the median bidimensional measurement of 14.2 (0.0–56.7) cm<sup>2</sup> in the TTField-treated phase III cohort (*P* = 0.6178; Table 1). However, 15 of 23 patients (65%) were already on bevacizumab before their neuroimaging studies, possibly interfering with tumour measurement because bevacizumab can reduce vascular permeability in tumours causing decreased gadolinium enhancement (Wong and Brem, 2008). Further, blockade of vascular endothelial growth factor can promote an invasive and diffuse glioblastoma phenotype that result in tumours possessing greater size than can be measured on gadolinium-enhanced T1-weighted MRI (Norden *et al*, 2008; Lu *et al*, 2012). We therefore measured the bidimensional size of the FLAIR abnormality. Indeed, in our cohort, the median bidimensional FLAIR abnormality was 29.6 (range 7.0–60.2) cm<sup>2</sup>, which is more than two times the tumour size observed on gadolinium-enhanced T1-weighted MRI in the phase III trial (Stupp *et al*, 2012). As expected, this bevacizumab effect on tumour measurement was corroborated in our entire patient cohort (*n* = 38) by the strong correlation between the size of the gadolinium-enhanced T1-weighted and FLAIR measured bidimensional tumour size among those not on bevacizumab (*r*<sup>2</sup> = 0.7333, *n* = 10; Supplementary Figure 1A), whereas no such correlation was seen among those on bevacizumab (*r*<sup>2</sup> = 0.1446, *n* = 27; Supplementary Figure 1B). Furthermore, we found that patients in our validation cohort who used dexamethasone > 4.1 mg per day (*n* = 4) had a worse outcome compared with the corresponding cohort in the phase III trial (*n* = 64), with a median OS of 3.2 months (95% CI: 1.2–NA) vs 4.8 months (95% CI: 3.9–6.0), respectively ( $\chi^2$  = 6.3, *P* = 0.0121; Figure 4D). Therefore, our single-institution validation cohort, who had KPS ≥ 70, used dexamethasone ≤ 4.1 mg per day and possessed greater tumour burden, compared favourably with those treated with TTFields therapy in the phase III trial, but those with KPS ≥ 70 but used

dexamethasone > 4.1 mg per day probably suffered from a worse outcome compared with the corresponding trial cohort.

**Patient immune characteristics and TTField therapy efficacy.** Dexamethasone has been associated with profound immunosuppression (Hughes *et al*, 2005; Grossman *et al*, 2011) and it may severely limit a patient’s ability to mount an antitumour immune response against the glioblastoma (Zitvogel *et al*, 2008a). Our data clearly demonstrated that dexamethasone doses higher than a threshold level of 4.1 mg per day correlated with a poorer patient outcome during TTField therapy. This finding strongly suggests an immunological component behind the efficacy of this intervention and that factors required for general immune competence may have a role in predicting therapeutic outcome in our patients. We therefore analysed their CD3<sup>+</sup>, CD4<sup>+</sup>, and CD8<sup>+</sup> T-lymphocyte subsets during the course of their treatment. Using the unsupervised binary partitioning approach described above for dexamethasone dose, we attempted to identify whether there was any threshold for the absolute CD3<sup>+</sup>, CD4<sup>+</sup>, or CD8<sup>+</sup> T-lymphocyte count, which yielded the greatest statistical difference in OS when used to stratify our patient population. Significantly, this analysis revealed that the median OS of patients with absolute CD3<sup>+</sup> ≤ 382 cells per mm<sup>3</sup> was 2.0 months (95% CI: 1.2–NA) (*n* = 7). In contrast, the median OS of those with CD3<sup>+</sup> > 382 cells per mm<sup>3</sup> was 7.6 months (95% CI: 4.3–13.9) (*n* = 22) ( $\chi^2$  = 17.8, *P* < 0.0001; Figure 5A), with the data showing that patient survival was positively correlated with the absolute numbers of CD3<sup>+</sup> T lymphocytes. Similarly, we found that patients with absolute CD4<sup>+</sup> ≤ 236 cells per mm<sup>3</sup> exhibited a median OS of 2.7 months (95% CI: 1.4–NA) (*n* = 9) as compared with those with CD4<sup>+</sup> > 236 cells per mm<sup>3</sup> with a median OS of 8.0 months (95% CI: 4.6–NA) (*n* = 20) ( $\chi^2$  = 13.4, *P* = 0.0002; Figure 5B). Furthermore, patients with an absolute CD8<sup>+</sup> count of ≤ 144 cells per mm<sup>3</sup> exhibited a median OS of 2.0 months (95% CI: 2.0–NA) (*n* = 5) as compared with 6.8 months (95% CI: 3.9–13.8) (*n* = 24) for those with CD8<sup>+</sup> > 144 cells per mm<sup>3</sup> ( $\chi^2$  = 8.1, *P* = 0.0045; Figure 5C). We next asked whether CD3<sup>+</sup>, CD4<sup>+</sup>, and CD8<sup>+</sup> lymphocyte counts was related to the overall status of the patient’s peripheral





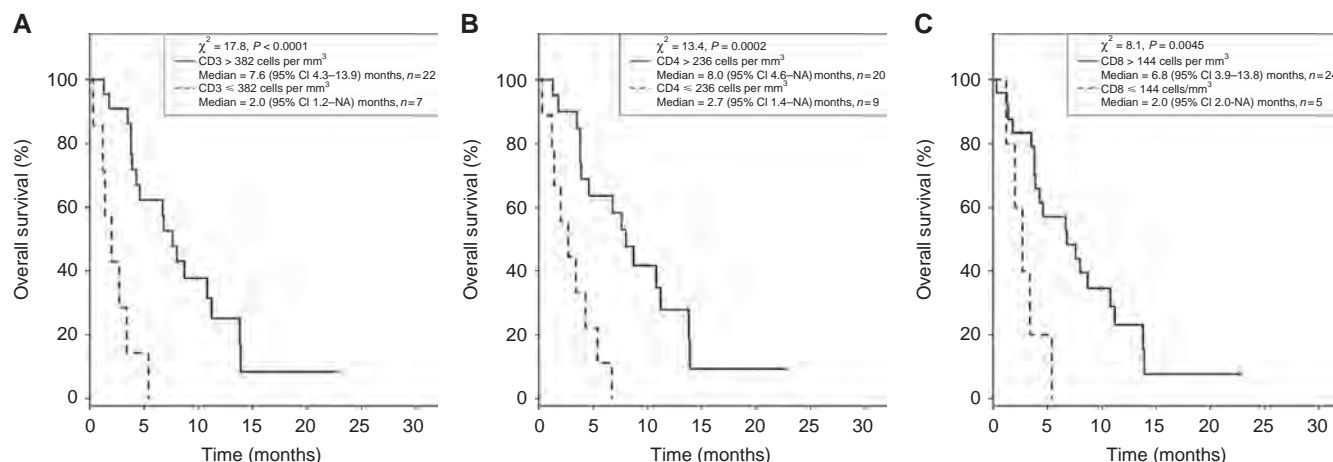
**Figure 4.** Kaplan–Meier estimates of survival in the validation cohort from a single institution. **(A)** The Kaplan–Meier survival curves for patients with KPS  $\geq 70$  (solid green) vs those with KPS  $< 70$  (solid black). **(B)** Dexamethasone effect on the cohort with KPS  $\geq 70$  by comparing patients taking dexamethasone  $\leq 4.1$  (solid green) vs those taking  $> 4.1$  mg per day (dashed green). **(C)** Comparison of the TTField-treated subjects who used  $\leq 4.1$  mg per day of dexamethasone in the phase III trial (from Figure 2A) vs the validation cohort with having KPS  $\geq 70$  and taking dexamethasone  $\leq 4.1$  mg per day. **(D)** Comparison of the TTField-treated subjects who used  $> 4.1$  mg per day of dexamethasone in the phase III trial (from Figure 2B) vs the validation cohort with having KPS  $\geq 70$  and taking dexamethasone  $> 4.1$  mg per day.

blood counts and dexamethasone requirement. As expected, there was a correlation between  $CD3^+$  and  $CD4^+$  cells ( $r^2 = 0.6949$ ) and between  $CD3^+$  and  $CD8^+$  cells ( $r^2 = 0.5001$ ) but not between  $CD4^+$  and  $CD8^+$  cells ( $r^2 = 0.0733$ ). However, there was no correlation between white blood cells (WBC) and  $CD3^+$  cells ( $r^2 = 0.0053$ ), WBC and  $CD4^+$  cells ( $r^2 = 0.0023$ ), and WBC and  $CD8^+$  cells ( $r^2 = 0.0032$ ). No correlation was also detected between platelets and  $CD3^+$  cells ( $r^2 = 0.2576$ ), platelets and  $CD4^+$  ( $r^2 = 0.2746$ ), and platelets and  $CD8^+$  ( $r^2 = 0.0887$ ). Similarly, there was no correlation between the daily dexamethasone dose and  $CD3^+$  cells ( $r^2 = 0.1888$ ), dexamethasone and  $CD4^+$  cells ( $r^2 = 0.1531$ ), and dexamethasone and  $CD8^+$  cells ( $r^2 = 0.0451$ ). Taken together,  $CD3^+$ ,  $CD4^+$ , and  $CD8^+$  lymphocyte counts appear to be independent of the peripheral blood counts and dexamethasone dose effect. Therefore, T-lymphocyte counts may serve as an independent measure of immunocompetence in our patients and predict treatment outcome when using NovoTTF-100A.

## DISCUSSION

Our previous *post hoc* analysis of responders in the phase III trial comparing NovoTTF-100A monotherapy and BPC chemotherapy for recurrent glioblastoma revealed that dexamethasone and prior low-grade glioma histology were predictors of response (Wong *et al*, 2014). Traditionally, oncologists view dexamethasone's influence on glioblastoma patients from the perspective of its antioedema effect from the tumour (Vecht *et al*, 1994), antiemetic efficacy against emetogenic chemotherapies, infections from its systemic immunosuppressive property (Vecht *et al*, 1994; Hughes *et al*, 2005), and changes in contrast enhancement on computed tomography (Chamberlain *et al*, 1988) or MRI (Ostergaard *et al*, 1999). Because dexamethasone has the potential to produce profound toxicities in patients in large part by suppressing their immune system and it is a clinically modifiable factor, we therefore extended our analysis of possible dexamethasone effect on outcome





**Figure 5.** Wilcoxon's rank-sum test of the optimal cutoff T-lymphocyte subsets as determined by an unsupervised binary partitioning algorithm. **(A)** Median OS of patients with absolute CD3<sup>+</sup> ≤ 382 vs > 382 cells per mm<sup>3</sup> was 2.0 months (range 0.3–5.4) (n = 7) and 7.7 months (range 1.3–22.7) (n = 25), respectively (P = 0.0017). **(B)** Median OS of patients with absolute CD4<sup>+</sup> ≤ 236 vs > 236 cells per mm<sup>3</sup> was 2.7 months (range 0.3–6.7) (n = 9) and 8.0 months (range 1.3–22.7) (n = 23), respectively (P = 0.0029). **(C)** Median OS of patients with absolute CD8<sup>+</sup> ≤ 144 vs > 144 cells per mm<sup>3</sup> was 2.7 months (range 1.2–5.4) (n = 5) and 7.6 months (range 0.3–22.7) (n = 27), respectively (P = 0.0313).

to the entire trial cohort. In this study, we have uncovered compelling evidence that dexamethasone counteracted the therapeutic efficacy of TTFields. Further, we also found that its use negatively correlated with survival in the cohort treated with chemotherapy. Our analysis is the first to show this significant impact of dexamethasone on treatment efficacy and patient OS, which is a discrete and unequivocal endpoint in contrast to progression-free survival or response for the conduct of clinical trials for recurrent glioblastomas.

In contrast to commonly used chemotherapeutic regimens, TTField monotherapy does not exert deleterious effects on the immune system, and thus, unlike the chemotherapy-treated cohort, TTField-treated subjects did not receive concurrent immunosuppressive agents other than dexamethasone during the entire trial period. Therefore, this trial provided us with a unique opportunity to examine the interference of dexamethasone on the clinical outcome of patients without the confounding influence of cytotoxic chemotherapies. Given our previous observation that responders from this trial had low dexamethasone usage (Wong *et al*, 2014), we first asked whether we could determine a threshold of dexamethasone exposure below which a benefit in patient survival could be detected within the entire cohort. Using an unsupervised mathematical algorithm, we found that a dexamethasone dose of 4.1 mg per day produced the greatest statistical segregation of OS in the TTField-treated cohort, and subjects who received > 4.1 mg per day had a 2.3-fold decrease in median OS compared with those who used ≤ 4.1 mg per day. Notably, using this dose level to stratify the control cohort treated with BPC chemotherapy also produced a statistically significant, but less robust, OS segregation, and subjects who received > 4.1 mg per day had a 1.5-fold decrease in median OS compared with those who used ≤ 4.1 mg per day. Within both cohorts, patients exhibited a decrease in OS starting at about 4.0 mg per day, with progressive decrement until a dosage of 8.0 mg per day, above which there was no further decrease in OS. Therefore, our data indicate that dexamethasone has a generalised and profound interference on treatment efficacy regardless of whether the treatment has non-cytotoxic or cytotoxic properties on the haematopoietic system.

Our analysis strongly indicates that dexamethasone interferes with the efficacy of both TTFields and BPC chemotherapies, the latter of which consisted largely of alkylating chemotherapies. In the sub-populations taking ≤ 4.1 mg per day of dexamethasone, 31 subjects treated with TTField monotherapy exhibited a better

outcome compared with the corresponding 40 subjects treated with BPC chemotherapy. This small but statistically significant benefit occurred within the first 11 months, after which the OS of the two cohorts overlapped and the benefit from TTField therapy dissipated. In contrast, for the sub-population taking > 4.1 mg per day of dexamethasone, 29 subjects treated with TTField monotherapy exhibited a worse outcome relative to the corresponding 22 subjects treated with BPC chemotherapy. Therefore, high dexamethasone dosage appears to negate or counteract the effect of both TTField therapy and BPC chemotherapy. Because the overall trial population in the TTField-treated cohort is only 120, the benefit of treatment in the 31 (26%) subjects taking ≤ 4.1 mg per day of dexamethasone is essentially negated by the hindrance caused by the 29 (24%) patients taking > 4.1 mg per day of dexamethasone when the populations were not segregated based on dexamethasone burden. This dexamethasone interference with TTField efficacy may explained the improved outcome seen in the trial for newly diagnosed glioblastoma patients (Stupp *et al*, 2014), who were not as severely affected by treatment effects when compared with recurrent glioblastoma patients who had a longer exposure to cytotoxic chemotherapy, dexamethasone, or both.

Our data also indicate that T-lymphocyte subsets may have an important role in the outcome of our validation cohort of patients treated with TTField therapy, with prolonged OS associated with absolute CD3<sup>+</sup> > 382 cells per mm<sup>3</sup>, CD4<sup>+</sup> > 235 cells per mm<sup>3</sup>, and CD8<sup>+</sup> > 144 cells per mm<sup>3</sup> in an unsupervised analysis. Hughes *et al* (2005) and Grossman *et al* (2011) both showed that dexamethasone induces a drop in CD4<sup>+</sup> lymphocyte count, which predisposes glioblastoma patients to infectious complications, and a CD4<sup>+</sup> count < 200 cells per mm<sup>3</sup> is associated with poor survival. However, we also noted that dexamethasone's immunosuppressive effect also blunted the therapeutic efficacy of TTField therapy and chemotherapy, probably as a result of its global interference with the patient's immune system. This notion is supported by our *in vitro* experiments, which demonstrated that cells attempting to divide in the presence of the TTFields are disrupted in mitosis during the metaphase-to-anaphase transition and experienced aberrant mitotic exit (Gera *et al*, 2015). These cells subsequently exhibited changes consistent with immunogenic cell death and thus were susceptible to immune elimination (Lee *et al*, 2011, 2013). Because subjects that received dexamethasone ≤ 4.1 mg per day in the phase III trial exhibited benefit from TTField therapy, the observed benefit is strongly consistent with an



increased immunogenicity of cells affected by TTFields. Furthermore, a number of cytotoxic chemotherapy agents, such as doxorubicin, 5-fluorouracil, and oxaliplatin, can induce either genomic or cytoplasmic stress in the tumour cell leading to immunogenic cell death (Zitvogel *et al*, 2008b). Although the extent of immunostimulatory effects of alkylators, such as lomustine, carmustine, procarbazine, and temozolomide is unknown, dacarbazine has been shown to upregulate NKG2D ligands on tumour cells and thereby target them for immune elimination by natural killer (NK) cells and CD8<sup>+</sup> cytotoxic T-lymphocytes (Hervieu *et al*, 2013). Furthermore, alkylating agents have been shown to induce the secretion of ATP and HMGB1, both of which are danger signals that can activate immune responses against dying cells (Zong *et al*, 2004). Lastly, in myeloma patients, dexamethasone can severely block lenalidomide-induced NK cell activation (Hsu *et al*, 2011). Taken together, there is a strong indication from our data that the cytotoxic agents used in the trial against recurrent glioblastomas also act by inducing immune responses against the tumour and that concurrent dexamethasone usage negated this benefit.

There are a number of limitations in the interpretation of our findings. First, our data only allowed us to examine global immunosuppression in our patients but provide no means to assess local immunosuppression within the tumour microenvironment. This local suppression of immune surveillance is thought to be mediated by arginase, regulatory T cells, and myeloid-derived immunosuppressive cells (Fecci *et al*, 2006; Jacobs *et al*, 2010; Raychaudhuri *et al*, 2011). Nevertheless, removal of global immunosuppressive factors is the first step towards successful antiglioblastoma therapy. Second, our T-lymphocyte analysis only measured cells in the adaptive immune system. However, TTField therapy and certain chemotherapy agents could potentially induce an NK cell response against the glioblastoma (Hervieu *et al*, 2013; Lee *et al*, 2013). However, the observed dexamethasone effect on absolute CD3<sup>+</sup>, CD4<sup>+</sup>, and CD8<sup>+</sup> lymphocytes could also negatively influence the activation of other cytotoxic subsets such as NK cells (Hsu *et al*, 2011). Therefore, future analysis of the specific effects of dexamethasone on glioblastoma treatment would need to include the global effect on these cells.

In conclusion, dexamethasone exerted a profound interference on the therapeutic effects of both TTField therapy and BPC chemotherapies. The threshold dose at which dexamethasone was able to be used with minimal interference on these treatments was 4.1 mg per day or lower. In our validation set of TTField-treated patients, the cluster that had the longest OS had CD3<sup>+</sup> > 382 cells per mm<sup>3</sup>, CD4<sup>+</sup> > 236 cells per mm<sup>3</sup>, and CD8<sup>+</sup> > 144 cells per mm<sup>3</sup>. Taken together, these data strongly suggest that the stimulation of immunity against the tumour operates in both of these therapeutic approaches. Future clinical trials for recurrent glioblastoma, as well as other types of brain tumours, may need to take into account the influence of dexamethasone on therapeutic outcome.

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## ORIGINAL RESEARCH

# Response assessment of NovoTTF-100A versus best physician's choice chemotherapy in recurrent glioblastoma

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## Keywords

NovoTTF-100A, recurrent glioblastoma, response

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## Abstract

The NovoTTF-100A device emits frequency-tuned alternating electric fields that interfere with tumor cell mitosis. In phase III trial for recurrent glioblastomas, NovoTTF-100A was shown to have equivalent efficacy and less toxicity when compared to Best Physician's Choice (BPC) chemotherapy. We analyzed the characteristics of responders and nonresponders in both cohorts to determine the characteristics of response and potential predictive factors. Tumor response and progression were determined by Macdonald criteria. Time to response, response duration, progression-free survival (PFS)  $\pm$  Simon–Makuch correction, overall survival (OS), prognostic factors, and relative hazard rates were compared between responders and nonresponders. Median response duration was 7.3 versus 5.6 months for NovoTTF-100A and BPC chemotherapy, respectively ( $P = 0.0009$ ). Five of 14 NovoTTF-100A responders but none of seven BPC responders had prior low-grade histology. Mean cumulative dexamethasone dose was 35.9 mg for responders versus 485.6 mg for nonresponders in the NovoTTF-100A cohort ( $P < 0.0001$ ). Hazard analysis showed delayed tumor progression in responders compared to nonresponders. Simon–Makuch-adjusted PFS was longer in responders than in nonresponders treated with NovoTTF-100A ( $P = 0.0007$ ) or BPC chemotherapy ( $P = 0.0222$ ). Median OS was longer for responders than nonresponders treated with NovoTTF-100A ( $P < 0.0001$ ) and BPC chemotherapy ( $P = 0.0235$ ). Pearson analysis showed strong correlation between response and OS in NovoTTF-100A ( $P = 0.0002$ ) but not in BPC cohort ( $P = 0.2900$ ). Our results indicate that the response characteristics favor NovoTTF-100A and data on prior low-grade histology and dexamethasone suggest potential genetic and epigenetic determinants of NovoTTF-100A response.

## Introduction

Patients with recurrent glioblastoma have poor prognosis. Objective response rates to alkylating chemotherapy are low, ranging 5–8% [1, 2]. Although bevacizumab has a remarkably high response rate of 25–60% [3], its ability to prolong the overall survival (OS) of patients in the recurrence setting is marginal and it still awaits testing in a randomized clinical trial [4, 5]. Those who failed

bevacizumab are unlikely to respond to subsequent therapy [6, 7]. Therefore, new and innovative therapies are needed for recurrent glioblastoma.

The NovoTTF-100A device is a novel cancer treatment that delivers low-intensity, intermediate frequency (200 kHz) tumor treating electric fields (TTFields) via transducer arrays applied onto the scalp. TTFields disrupt glioblastoma cells during mitosis, resulting in apoptosis, aneuploidy, asymmetric chromosome segregation, and



defects in centrioles and mitotic spindles [8–10]. In a phase III trial for recurrent glioblastoma, this device has been shown to have equivalent efficacy when compared to conventional chemotherapies, including bevacizumab [11]. Notably, the NovoTTF-100A cohort had more responders than the Best Physician's Choice (BPC) chemotherapy cohort [11, 12] and NovoTTF-100A responders may offer insights into the mechanisms of action of TTFields on glioblastoma. Therefore, we undertake this post hoc analysis on the characteristics between responders in the NovoTTF-100A and BPC cohorts, as well as differences between responders and nonresponders within each cohort.

## Patients and Methods

### Patients

The conduct and the overall results of the pivotal phase III trial were previously published [11] and outlined in the CONSORT diagram (Fig. 1). Tumor response and progression were determined according to Macdonald criteria [13] and confirmed by independent radiology review.

### Statistical analysis

The corresponding author has full access to the data and is responsible for the outcome of analysis. Kaplan–Meier distributions [14] were generated using the R statistical package ([www.r-project.org](http://www.r-project.org)). The median, 95% confidence interval (95% CI), and *P* values were computed for time to response and response duration for responders in both NovoTTF-100A and BPC chemotherapy cohorts. Prognostic factors were compared between groups using Wilcoxon rank-sum test.

To examine whether NovoTTF-100A had a greater or weaker efficacy over BPC chemotherapy, we computed the relative density of hazard rates for responders and nonresponders to determine an increasing or decreasing rate of tumor progression [15, 16]. Plots of hazard rate density as a function of time to tumor progression were generated using R.

OS and progression-free survival (PFS) between responders and nonresponders were analyzed using Kaplan–Meier statistics [14]. Additional PFS analysis was done to minimize potential bias in the responder population by introducing the Simon–Makuch correction [17, 18]. This was done by adding the median time to response to both responders' response duration and nonresponders' time to progression, followed by derivation of Kaplan–Meier distributions. The median PFS and 95% CI were computed in the adjusted groups and independence was tested by chi-squared statistics.

The distribution of OS was also compared to time to response and response duration. Linear regression was fitted to determine a one-to-one relationship between the two time intervals and the  $r^2$  value was computed. Pearson rank coefficient was computed to determine the strengths of the correlation. A scatter plot of the two time intervals was generated in R and independence was tested by chi-squared statistics.

## Results

### Responder characteristics

The NovoTTF-100A cohort ( $N = 120$ ) had more responders than the BPC cohort ( $N = 117$ ) (Table 1). The respective median time to response was 8.4 (95% CI 6.9–9.9) months in the NovoTTF-100A responders and 5.8 (95% CI 3.6–8.0) months in the BPC chemotherapy

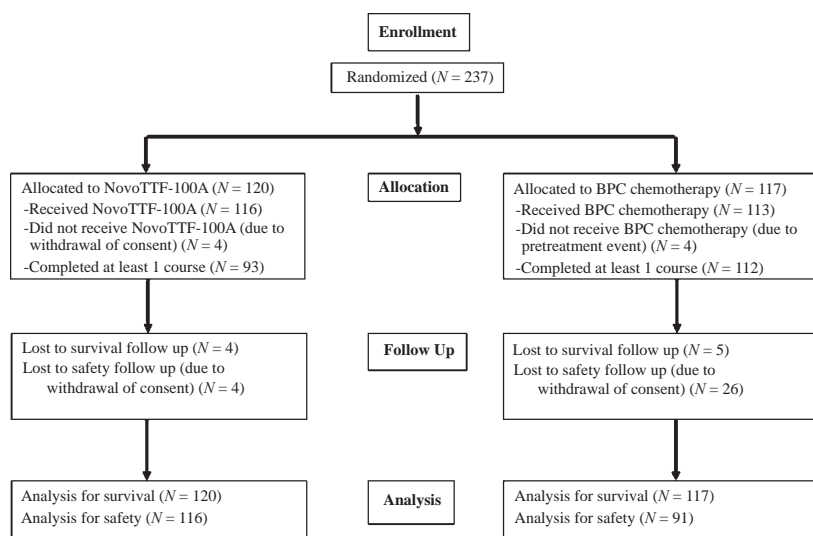


Figure 1. CONSORT diagram.



responders ( $P = 0.5755$ , Figs. 2 and 3). Six of 14 responders (43%) had initial growth of the tumor at 2–24 months while on NovoTTF-100A suggesting a period of tumor pseudoprogression. The median response duration was 7.3 (95% CI 0.0–16.6) and 5.6 (95% CI 3.8–7.5) months, respectively ( $P = 0.0009$ ). These data indicate that, compared to BPC chemotherapy responders, the NovoTTF-100A responders may have had a longer time to response after treatment initiation and, when responded, they had a more durable response.

**Table 1.** Clinical and response characteristics of NovoTTF-100A versus BPC chemotherapy cohorts.

	NovoTTF-100A ( <i>N</i> = 14 of 120)	BPC chemotherapy ( <i>N</i> = 7 of 117)
<b>Clinical characteristics</b>		
Age, median (range)	54 (36–75)	50 (35–59)
KPS, median (range)	90 (60–100) %	80 (60–100) %
Tumor size, median (range)	13 (2–38) cm <sup>2</sup>	14 (5–44) cm <sup>2</sup>
Prior low-grade glioma	5 (36%)	0 (0%)
Median time from diagnosis	8.3 months	11.8 months
Duration of device usage, median (range)	22 (13–23) h/day	Not applicable
Daily dexamethasone dose, median (range)	0.5 (0.0–12.0) mg	3.0 (0.0–18.0) mg
<b>Response characteristics</b>		
Complete response	3 (3%)	0 (0%)
Partial response	11 (9%)	7 (6%)
Median (95% CI) time to response	8.4 (6.9–9.9) months	5.8 (3.6–8.0) months
	$P = 0.5755$	
Median (95% CI) response duration	7.3 (0.0–16.6) months	5.6 (3.8–7.5) months
	$P = 0.0009$	
<b>Median (95% CI) unadjusted PFS</b>		
Responders	14.8 (11.0–N/A) months	11.3 (9.4–N/A) months
Nonresponders	2.1 (2.0–2.2) months	2.1 (2.0–2.8) months
$\chi^2$	25.5 ( $P < 0.0001$ )	16.5 ( $P < 0.0001$ )
<b>Median (95% CI) Simon–Makuch adjusted PFS</b>		
Responders	17.8 (11.5–N/A) months	11.5 (11.4–N/A) months
Nonresponders	10.5 (10.4–10.6) months	7.9 (7.8–8.6) months
$\chi^2$	11.5 ( $P = 0.0007$ )	5.2 ( $P = 0.0222$ )
<b>Median (95% CI) OS</b>		
Responders	24.8 (17.5–N/A) months	20.0 (14.5–N/A) months
Nonresponders	6.2 (5.0–7.7) months	6.8 (5.8–8.5) months
$\chi^2$	25.7 ( $P < 0.0001$ )	5.1 ( $P = 0.0235$ )

BPC, Best Physician's Choice;  $\chi^2$ , chi-squared; CI, confidence interval; N/A, not available; OS, overall survival; PFS, progression-free survival.

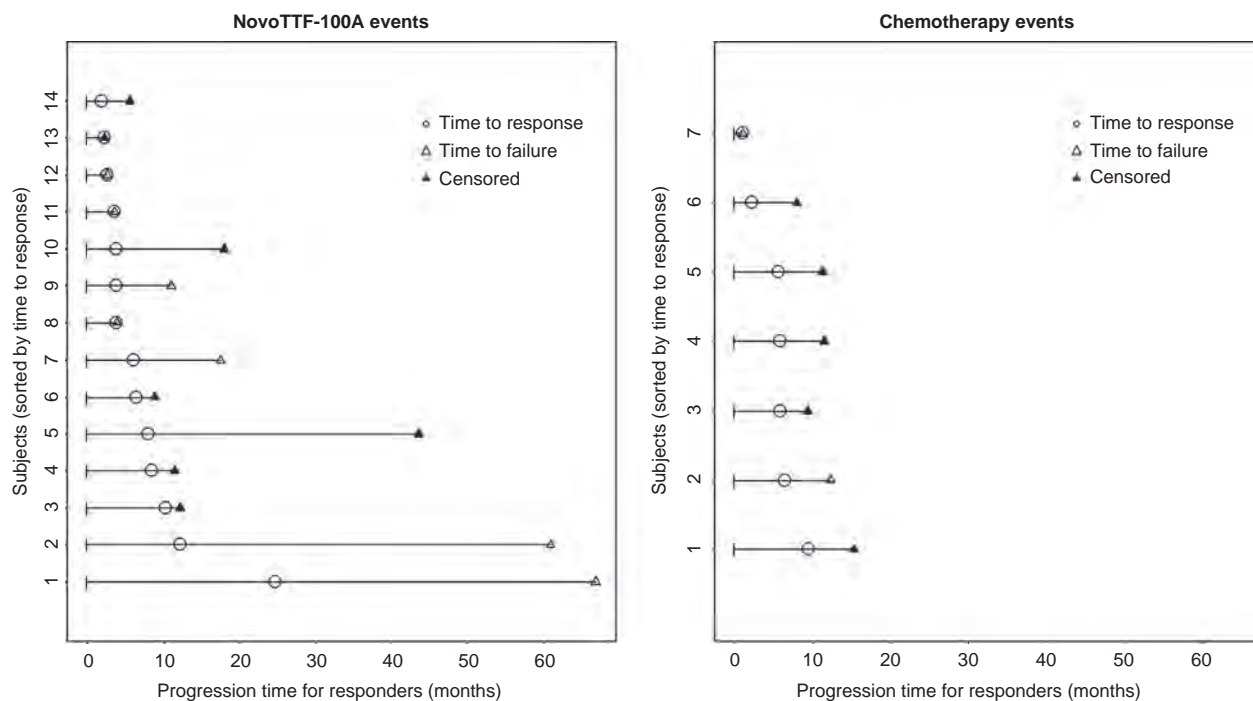
NovoTTF-100A responders have somewhat different clinical characteristics than BPC responders (Table 1). Notably, five of 14 responders in the NovoTTF-100A cohort, while none of seven responders in the BPC cohort, had prior low-grade histology. Among the NovoTTF-100A responders, there was a trend for increased median and mean OS among those with prior low-grade histology compared to those without, 27.7 and 39.2 (95% CI 19.0–59.4) versus 16.6 and 17.0 (95% CI 9.1–24.9) months, respectively ( $P = 0.0532$ , Fig. 4A). However, the median and mean PFS was significantly prolonged among those with prior low-grade histology compared to those without, 18.0 and 34.4 (95% CI 10.6–58.3) versus 5.5 and 10.7 (95% CI 2.2–19.2) months, respectively ( $P = 0.0278$ , Fig. 4B).

Dexamethasone use among responders was also significantly lower than that in nonresponders (Fig. 5). In both NovoTTF-100A and BPC cohorts, responders had a lower daily dexamethasone usage than nonresponders. For the NovoTTF-100A cohort, the respective median and mean daily dexamethasone dose was 1.0 and 2.3 (95% CI 0.8–3.8) mg for responders versus 5.2 and 6.8 (95% CI 5.6–8.1) mg for nonresponders ( $P = 0.0019$ ). For the BPC chemotherapy cohort, the respective median and mean daily dexamethasone dose was 1.2 and 1.4 (95% CI 0.3–2.4) mg for responders versus 6.0 and 7.2 (95% CI 6.0–8.4) mg for nonresponders ( $P = 0.0041$ ). Notably, the cumulative dexamethasone dose was only found to be significantly lower in responders than nonresponders in the NovoTTF-100A cohort but not in the BPC chemotherapy cohort. For the NovoTTF-100A cohort, the respective median and mean cumulative dexamethasone dose was 7.1 and 35.9 (95% CI N/A–72.5) mg for responders versus 261.7 and 485.6 (95% CI 347.9–623.4) mg for nonresponders ( $P < 0.0001$ ). For the BPC chemotherapy cohort, the respective median and mean cumulative dexamethasone dose was 348.5 and 525.6 (95% CI 96.5–954.7) mg for responders versus 242.3 and 431.0 (95% CI 328.1–533.8) mg for nonresponders ( $P = 0.9520$ ). Therefore, in light of the more frequent low-grade histology and the lower cumulative dexamethasone dose, NovoTTF-100A responders may have more favorable genetic and/or epigenetic characteristics. [Correction added on 30th May 2014, after first online publication: “daily” was amended to “cumulative” in the median and mean dexamethasone dose for the BPC chemotherapy cohort. The same has been amended in the legend of Figure 5, section D.]

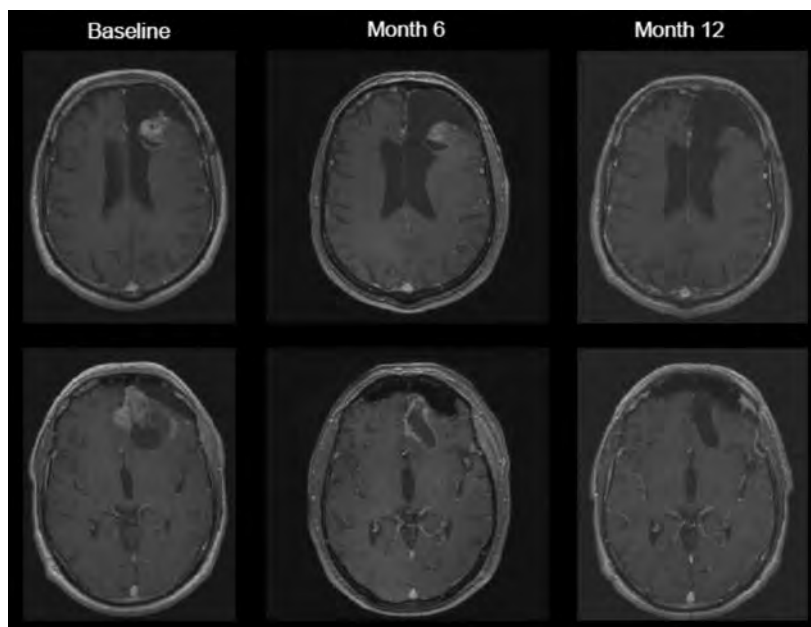
### Hazard analysis in responders and nonresponders

The hazard rate of tumor progression initially increased with time, reached a maximum, and then fell to a basal rate in both responders and nonresponders (Fig. 6). However, for NovoTTF-100A responders, the peak hazard





**Figure 2.** Event chart for responders in the NovoTTF-100A and BPC chemotherapy cohorts. Each line represents a single patient and patients are sorted according to the time to response. Transition between states, that is response and failure, are indicated by the corresponding symbols represented on the time line. BPC, Best Physician's Choice.

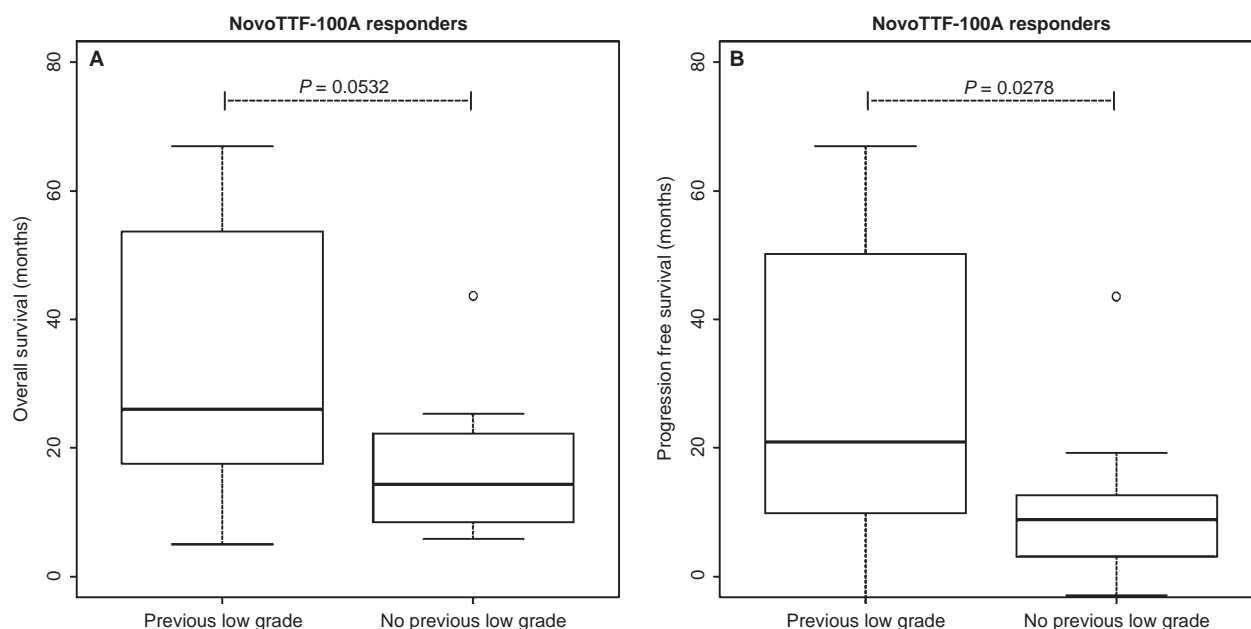


**Figure 3.** MRI from a complete responder treated with NovoTTF-100A monotherapy. Partial response was noted only after 6 months and complete response was noted after 12 months. MRI, magnetic resonance imaging.

rate was lower than that for nonresponders and the time of peak hazard rate was delayed compared to nonresponders. The proportional hazard ratio was 0.1560 (95%

CI 0.0698–0.3500,  $P < 0.0001$ ). In contrast, the BPC cohort's hazard rate for responders peaked higher compared to nonresponders, while the time of peak hazard





**Figure 4.** Box-and-whisker plot of OS and PFS of responders in the NovoTTF-100A cohort with and without prior low-grade glioma histology. (A) The median and mean OS was 27.7 and 39.2 (95% CI 19.0–59.4) months among responders with prior low-grade histology compared to 16.6 and 17.0 (95% CI 9.1–24.9) months among those without prior low-grade histology ( $P = 0.0532$ ). (B) The median and mean PFS was significantly prolonged among responders with prior low-grade histology, 18.0 and 34.4 (95% CI 10.6–58.3) months, compared to those without, 5.5 and 10.7 (95% CI 2.2–19.2) months ( $P = 0.0278$ ). The central boxes represent values from first to third quartile (25–75th percentiles). The horizontal line represents the median and the vertical line extends from the minimum to maximum values and shows the presence of outlier. The outlier was not excluded from analysis. OS, overall survival; PFS, progression-free survival; CI, confidence interval.

rate is also delayed in responders compared to nonresponders. The proportional hazard ratio was 0.0877 (95% CI 0.0208–0.3700,  $P = 0.0009$ ). The results in both cohorts indicate that responders had a delay in tumor progression, but the higher peak hazard rate in the BPC cohort may be due to their tumor progression at nearly simultaneous time.

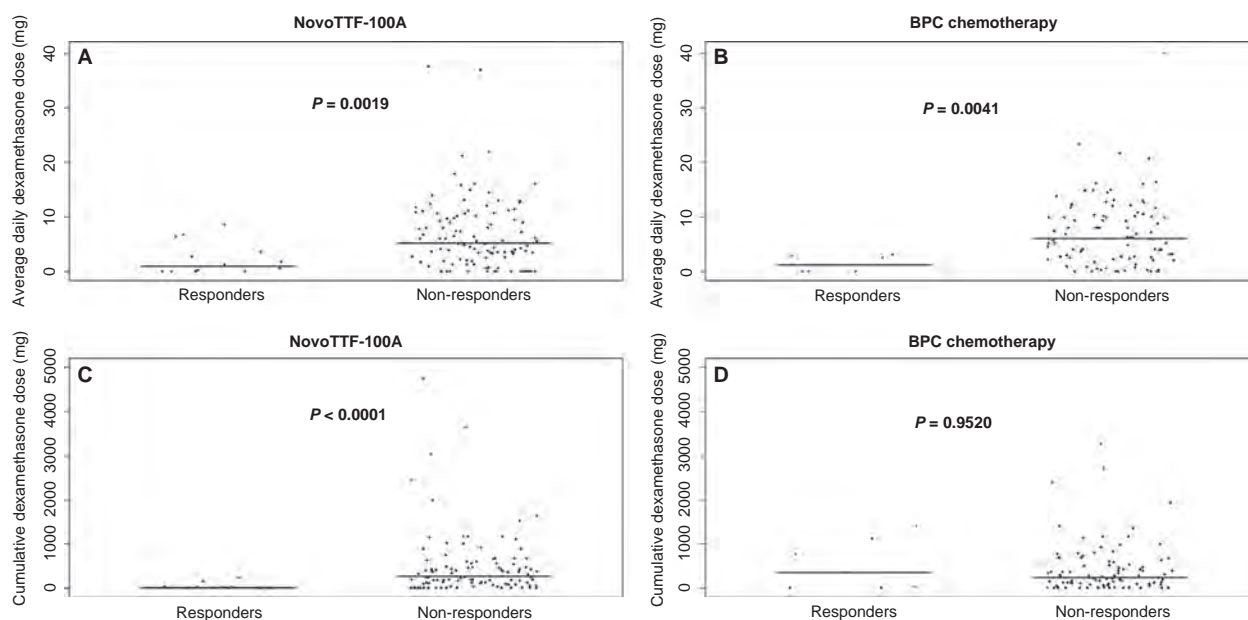
### Survival analysis in responders and nonresponders

Because responders inherently have a longer period of progression-free state due to the presence of the time-to-response state, adjustment is needed to correct the start time when comparing PFS in responders and nonresponders (Table 1 and Fig. 7). Indeed, in unadjusted analyses for both cohorts, responders had marked prolongation of PFS than nonresponders. To correct this apparent bias, we used the Simon–Makuch adjustment to generate conditional PFS plots [17, 18] (Fig. 8). The conditioning time was adjusted based on the Kaplan–Meier estimate of the median time to response in the respective responder groups, or 8.4 months for the NovoTTF-100A versus 5.8 months for the BPC chemotherapy cohort. The adjusted analysis showed that in the NovoTTF-100A

cohort, the median Simon–Makuch conditional PFS was 17.8 (95% CI 11.5–N/A) months for responders and 10.5 (95% CI 10.4–10.6) months for nonresponders ( $\chi^2 = 11.5$ ,  $P = 0.0007$ ). In the BPC chemotherapy cohort, the corresponding conditional PFS was 11.5 (95% CI 11.4–N/A) months for responders and 7.9 (95% CI 7.8–8.6) months for nonresponders ( $\chi^2 = 5.2$ ,  $P = 0.0222$ ). After correcting for bias, responders still had a longer adjusted PFS than nonresponder and this difference was unlikely due to chance. This difference was also notably greater in the NovoTTF-100A than the BPC cohort.

In OS analysis (Fig. 9), responders treated with either NovoTTF-100A or BPC chemotherapy did better than nonresponders. The median OS was 24.8 (95% CI 17.5–N/A) months for responders and 6.2 (95% CI 5.0–7.7) months for nonresponders in the NovoTTF-100A cohort ( $\chi^2 = 25.7$ ,  $P < 0.0001$ ), while it was 20.0 (95% CI 14.5–N/A) months for responders and 6.8 (95% CI 5.8–8.5) months for nonresponders in the BPC cohort ( $\chi^2 = 5.1$ ,  $P = 0.0235$ ). Because responders were expected to live longer than nonresponders, we next asked whether the time to response or the response duration would correlate with OS in either cohort. In the time to response versus OS analysis, the NovoTTF-100A cohort had a linear regression coefficient of  $r^2 = 0.698$  and a Pearson correla-





**Figure 5.** Scatter plot of mean daily dexamethasone and cumulative dexamethasone dose in responders and nonresponders. (A) In the NovoTTF-100A cohort, the respective median and mean daily dexamethasone dose was 1.0 and 2.3 (95% CI 0.8–3.8) mg for responders versus 5.2 and 6.8 (95% CI 5.6–8.1) mg for nonresponders ( $P = 0.0019$ ). (B) In the BPC cohort, the respective median and mean daily dexamethasone dose was 1.2 and 1.4 (95% CI 0.3–2.4) mg for responders versus 6.0 and 7.2 (95% CI 6.0–8.4) mg for nonresponders. (C) In the NovoTTF-100A cohort, the respective median and mean cumulative dexamethasone dose was 7.1 and 35.9 (95% CI N/A–72.5) mg for responders versus 261.7 and 485.6 (95% CI 347.9–623.4) mg for nonresponders ( $P < 0.0001$ ). (D) In the BPC cohort, the respective median and mean cumulative dexamethasone dose was 348.5 and 525.6 (95% CI 96.5–954.7) mg for responders versus 242.3 and 431.0 (95% CI 328.1–533.8) mg for nonresponders ( $P = 0.9520$ ). BPC, Best Physician's Choice; CI, confidence interval; N/A, not available.

tion coefficient of  $\rho = 0.8356$  ( $P = 0.0002$ ), suggesting a strong correlation between these two parameters. No such correlation was seen in the BPC cohort,  $r^2 = 0.217$  and  $\rho = 0.4676$  ( $P = 0.2900$ ). Similarly, in the response duration versus OS analysis, the NovoTTF-100A cohort had a linear regression coefficient of  $r^2 = 0.923$  and a Pearson correlation coefficient of  $\rho = 0.9608$  ( $P < 0.0001$ ). Again, no such correlation was seen in the BPC cohort,  $r^2 = 0.0566$ ,  $\rho = 0.2282$  ( $P = 0.6226$ ). In addition, we used chi-squared distribution analysis to further investigate whether or not there was an association between OS and response. We found no statistical difference between OS and time to response ( $\chi^2 = 336.0$ ,  $P = 0.3114$ ) as well as between OS and response duration ( $\chi^2 = 257.2$ ,  $P = 0.3967$ ), suggesting that OS and response were related parameters. Together, our data indicated that there was a correlation between response and OS and this effect was predominantly seen in the NovoTTF-100A cohort.

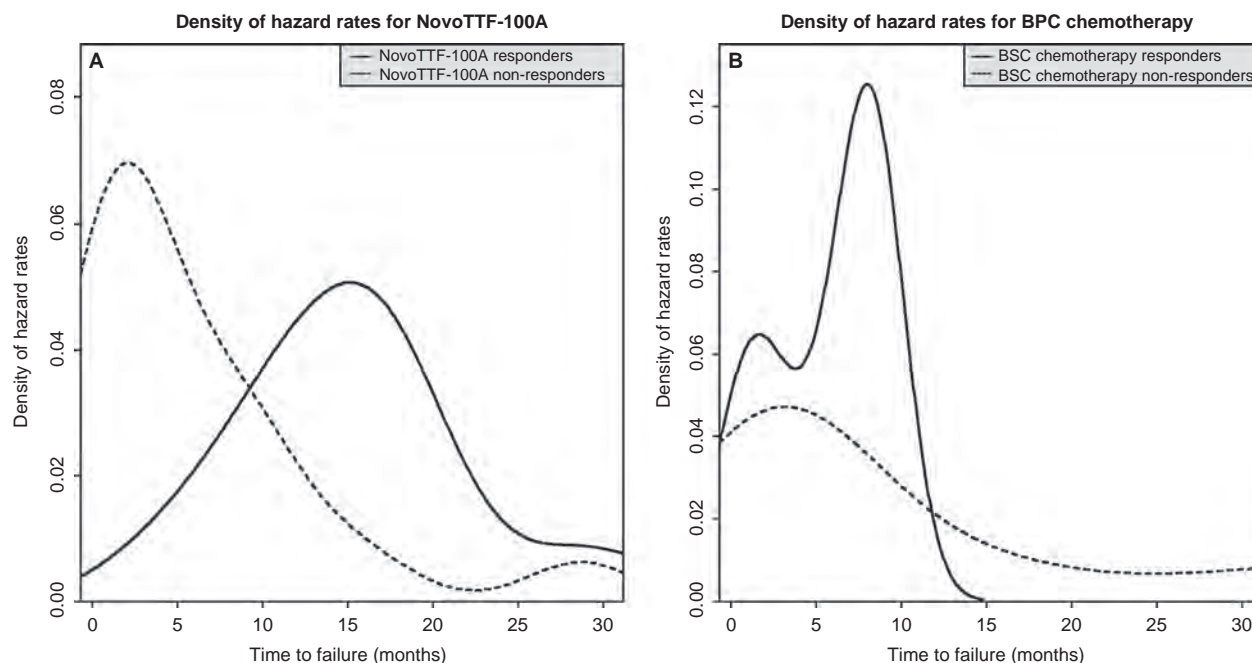
## Discussion

Response is typically a secondary endpoint in cancer clinical trials and, when present, it usually signifies antitumor activity. However, bona fide response may or may not correlate with improved survival for recurrent glioblastoma.

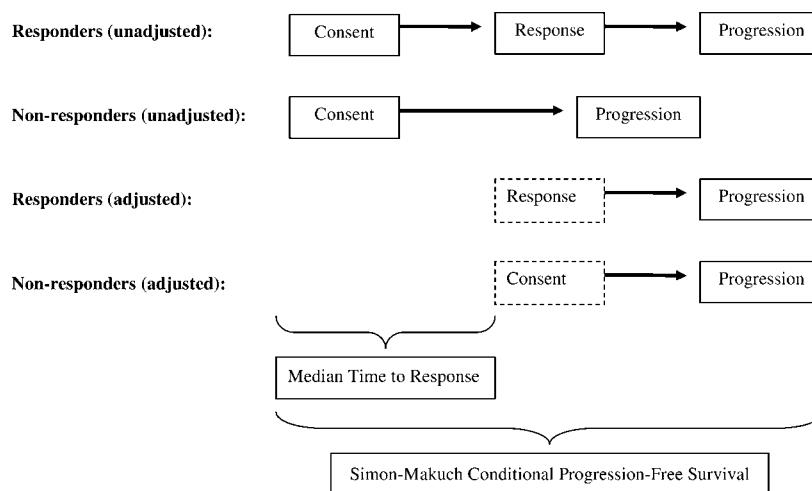
A good example is antiangiogenesis drug like bevacizumab, which has a response rate of 25–60% and a 6-month PFS of 45% primarily from nonrandomized, single-arm phase II trials [3]. However, it has limited impact on OS [4, 5]. In contrast, a randomized trial of temozolomide versus procarbazine detected only six of 112 (5.4%) versus six of 113 (5.3%) responders, respectively, but the PFS and OS at 6 months were significantly different, 21% and 8% versus 60% and 44%, respectively [2]. This lack of concordance between response and survival probably stems from the low efficacy of single-agent cytotoxic chemotherapy against recurrent glioblastoma [19], which has a plethora of resistant clones endowed with genetic and/or epigenetic derangements. Interestingly, bevacizumab was approved for recurrent glioblastoma based on single-arm, phase II response data while temozolomide was rejected despite positive survival data, indicating that response remains important in the overall efficacy analysis.

Our analysis showed that responders in the two cohorts have different clinical characteristics. First, in the prior phase III trial, 10 of 120 (8%) subjects in the NovoTTF-100A cohort and nine of 117 (8%) subjects in the BPC cohort had prior low-grade histologies [11]. However, a significantly higher proportion of NovoTTF-100A





**Figure 6.** The hazard functions for tumor progression in responders and nonresponders. This is a time-dependent estimate of responders that transition out of response into tumor progression or nonresponders that directly transition into tumor progression. (A) In the NovoTTF-100A cohort, the peak hazard rate for responders is lower than that for nonresponders, 0.051 versus 0.069, respectively, and the time of peak hazard rate is delayed in responders compared to nonresponders, 15.1 versus 1.9 months, respectively. (B) In the BPC chemotherapy cohort, the peak hazard rate for responders is higher than that for nonresponders, 0.125 versus 0.047, respectively, but the time of peak hazard rate is still delayed in responders compared to nonresponders, 8.0 versus 3.1 months, respectively. The higher peak hazard rate for responders could be a result of the small sample size ( $N = 7$ ) and/or most patients go into tumor progression at nearly simultaneous time. BPC, Best Physician's Choice.

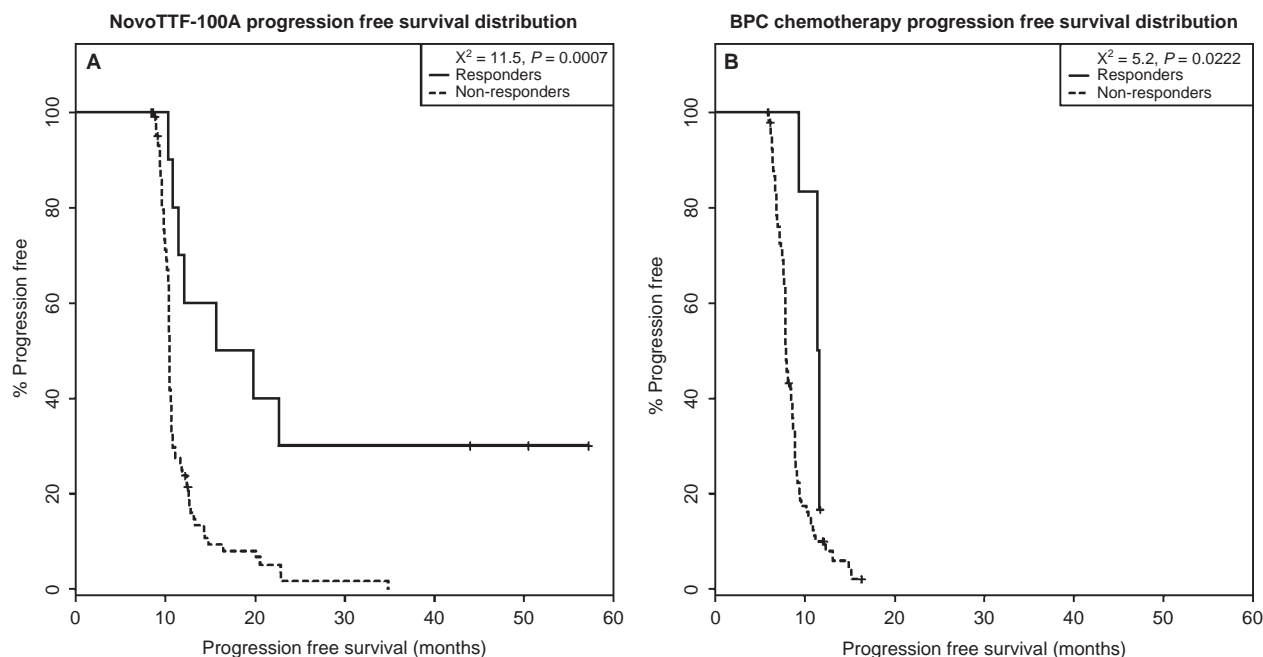


**Figure 7.** Graphical representation of the adjusted Simon-Makuch conditional PFS. In the intent-to-treat population, PFS is measured from the time of consent until progression or censored event. However, responders pass through a state from consent to response and this time-to-response period introduces a bias in the statistical comparison of responders versus nonresponders, favoring the responder group. To correct this bias, the median time to response is added to both responder and nonresponder groups before comparison of the respective PFS distributions. PFS, progression-free survival.

responders, five of 14 (36%), had prior low-grade histologies while none of seven (0%) BPC responder had this type of histological characteristics, suggesting that

secondary glioblastoma may be more responsive to NovoTTF-100A treatment. Because primary and secondary glioblastomas have different genetic alterations, notably



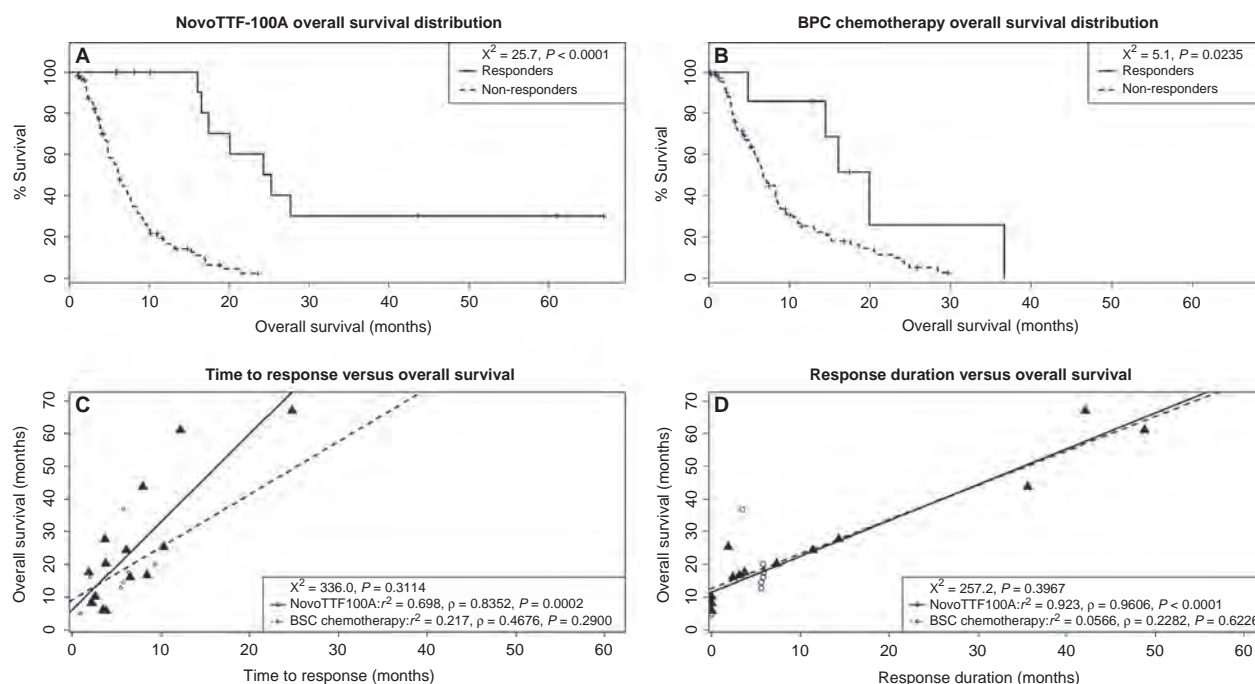


**Figure 8.** Simon-Makuch conditional PFS distribution. The PFS distribution remains significant after adjustment. (A) In the NovoTTF-100A cohort, the median adjusted PFS is 17.8 (95% CI 11.5–N/A) months for responders and 10.5 (95% CI 10.4–10.6) months for nonresponders. Compared to the value before adjustment, the chi-squared distribution between the two groups remained significant at 11.5 ( $P = 0.0007$ ). (B) In the BPC chemotherapy cohort, the median adjusted PFS is 11.5 (95% CI 11.4–N/A) months for responders and 7.9 (95% CI 7.8–8.6) months for nonresponders. Compared to the value before adjustment, the chi-squared distribution between these two groups also remained significant at 5.2 ( $P = 0.0222$ ). PFS, progression-free survival; CI, confidence interval; N/A, not available; BPS, Best Physician's Choice.

*EGFR* and *MDM2* amplifications together with *p16* deletion in primary glioblastomas and *p53* mutation, *IDH1* mutation and *PDGFR* amplification in secondary glioblastomas, the distinct genetic makeup in these two subtypes of glioblastomas could make secondary glioblastomas more susceptible to NovoTTF-100A treatment [20, 21]. In the genomic analysis of glioblastoma subtypes, Verhaak et al. [21] found that the majority of secondary glioblastomas have proneural profiles expressing oligodendrocytic development genes such as *PDGFRA* and *OLIG2*. Notably, the proneural subtype is less responsive to concurrent chemotherapy and radiation than the classical, mesenchymal, and neural subtypes [21]. Similarly, Ducray et al. reported that there was no significant response to neoadjuvant chemotherapy or radiation alone in the proneural glioblastoma while the mesenchymal and classical subtypes were more likely to respond to radiation and chemotherapy, respectively [22]. Therefore, it would be important to determine whether the five NovoTTF-100A responders with previous low-grade histologies also have gene expression profile consistent with the proneural form, as opposed to other subtypes, of glioblastoma. Furthermore, nine of 14 (64%) responders in the

NovoTTF-100A cohort had no prior low-grade histology and the response seen in these patients may suggest that there could be additional genetic and/or epigenetic determinants. Second, the daily dexamethasone dose used by both NovoTTF-100A and BPC chemotherapy responders was significantly lower than that used by nonresponders. Indeed, dexamethasone has been associated with profound immunosuppression and increased risk of infection [23]. More importantly, patients with lower dexamethasone usage may be more able to mount an anticancer immune response against the glioblastoma [24, 25]. Our preclinical data indicate that alternating electric fields stress the cytoplasm of dividing tumor cells and that cause the translocation of calreticulin from the endoplasmic reticulum to the surface of cell membrane [25, 26]. This surface expression of calreticulin could mark the tumor cells for immune destruction. Therefore, this type of antiglioblastoma immune response may be more important for NovoTTF-100A responders than BPC chemotherapy responders, as global immunosuppression by dexamethasone plays a greater role in counteracting the efficacy of NovoTTF-100A than BPC chemotherapy. Taken together, the data on prior low-grade histology





**Figure 9.** Overall survival distribution between responders and nonresponders. (A) In the NovoTTF-100A cohort, the median OS is 24.8 (95% CI 17.5–N/A) months for responders and 6.2 (95% CI 5.0–7.7) months for nonresponders, and the chi-squared distribution between these two groups is significantly different at 25.7 ( $P < 0.0001$ ). (B) In the BPC chemotherapy cohort, the median OS is 20.0 (95% CI 14.5–N/A) months for responders and 6.8 (95% CI 5.8–8.5) months for nonresponders. The chi-squared distribution between these two groups has a smaller difference at 5.1 ( $P = 0.0235$ ). (C) In the NovoTTF-100A cohort, there is linearity and correlation between OS and time to response (linear regression  $r^2 = 0.698$ ; Pearson  $\rho = 0.8352$ ,  $P = 0.0002$ ). However, in the BPC cohort, the linearity and correlation are less robust between OS and time to response (linear regression  $r^2 = 0.217$ ; Pearson  $\rho = 0.4676$ ,  $P = 0.2900$ ). In the chi-squared distribution analysis, there is no statistical difference between OS and time to response ( $\chi^2 = 336.0$ ,  $P = 0.3114$ ), suggesting that OS and time to response are statistically related parameters. (D) In the NovoTTF-100A cohort, there is also linearity and correlation between OS and response duration (linear regression  $r^2 = 0.923$ ; Pearson  $\rho = 0.9606$ ,  $P < 0.0001$ ). However, in the BPC cohort, there is no linearity or correlation between OS and response duration (linear regression  $r^2 = 0.0566$ ; Pearson  $\rho = 0.2282$ ,  $P = 0.6226$ ). In the chi-squared distribution analysis, there is no statistical difference between OS and response duration ( $\chi^2 = 257.2$ ,  $P = 0.3967$ ), suggesting that OS and response duration are statistically related parameters. CI, confidence interval; BPS, Best Physician's Choice; N/A, not available;  $\chi^2$ , chi-squared.

and dexamethasone dose suggest potential underlying genetic and/or epigenetics determinants of NovoTTF-100A response.

The response duration, adjusted Simon–Makuch PFS, and OS favor NovoTTF-100A over BPC chemotherapy. First, responders in our NovoTTF-100A cohort behaved similar to a prior analysis by Hess et al. [18], with the hazard rate peaking lower and later than the nonresponders. However, responders in the BPC cohort peaked markedly higher than nonresponders, which could be a result of near-simultaneous tumor progression. Furthermore, the time interval between peak hazard rates of responders and nonresponders in the BPC cohort is narrower than that for the NovoTTF-100A cohort, suggesting that NovoTTF-100A responders had a slightly more favorable tumor progression profile than BPC chemotherapy responders. Second, Simon and Makuch [17, 18] introduced a correction by adding the median time

to response for every patient in both responder and nonresponder groups and thereby removing the inherent bias in responders when performing survival comparison. Compared to the unadjusted PFS analysis, the Simon–Makuch adjustment showed a smaller but still significant difference in the chi-squared distributions between responders and nonresponders in both NovoTTF-100A and BPC cohorts. Therefore, the difference in PFS between NovoTTF-100A responders and nonresponders remains statistically valid despite the small sample size of responders. Also, this difference is larger in the NovoTTF-100A than the BPC cohort, suggesting that responders possibly experienced a greater efficacy from NovoTTF-100A than responders from BPC chemotherapy. Lastly, we showed an association between survival and response. Our chi-squared analysis cannot reject the null hypothesis that OS versus time to response and OS versus response duration are different in our two cohorts.



Notably, Pearson analysis showed that responders to NovoTTF-100A had a stronger correlation than responders to BPC chemotherapy. Hess et al. [16] used Cox proportional hazard analysis of responders to cytotoxic chemotherapies and also found a correlation between OS and response. Together, these data suggest that NovoTTF-100A responders have longer OS and PFS, but a larger sample size is needed to confirm this finding.

There are multiple challenges facing the development of drug therapies for glioblastoma, including parallel and redundant signaling pathways that subserve the growth and proliferation of the tumor, multiple pharmacodynamic targets, the narrow therapeutic index, propensity for the development of resistance, and pharmacokinetic interference from the blood–brain barrier. Therefore, novel treatments that can overcome these challenges are needed. The NovoTTF-100A device fits this profile because it is a locoregional therapy and thereby lacks systemic side effects. Similar to traditional cytotoxic chemotherapies and newer targeted agents, it also interferes with tumor cell mitosis. Specifically, the alternating electric fields emitted by the device block tumor cell progression from metaphase to anaphase, resulting in chromosomal aneuploidy and cytoplasmic stress that ultimately lead to apoptosis, immunogenic cell death, or both [10, 26]. In this post hoc analysis comparing responders in the NovoTTF-100A and BPC chemotherapy cohorts, we found that secondary glioblastomas and low dexamethasone usage are associated with a higher proportion of NovoTTF-100A responders but not BPC chemotherapy responders. It is notable that in a population-based study performed by Ohgaki et al. [27], secondary glioblastomas appeared to have a slower rate of decline in survival than primary glioblastomas. We speculate that patients whose glioblastomas arose from prior low-grade gliomas may have a slower growth rate than those from primary glioblastomas. When treated with NovoTTF-100A, this slower rate of tumor progression might allow enough time for the efficacy of TTFs to emerge because it may take multiple mitotic cycles to reduce the number of tumor cells and the size of the glioblastoma. This slower rate of growth may not matter as much for BPC chemotherapies due to their direct genomic toxicity. Furthermore, the cytoplasmic stress induced by the alternating electric fields also marks the tumor cells for immunological destruction and clearance [26]. Therefore, removal of immunosuppression in the patient, such as reducing or discontinuing dexamethasone usage, would have a greater effect on those receiving NovoTTF-100A treatment than BPC chemotherapy. Taken together, a possible slower rate of tumor growth in secondary glioblastomas and a reduction in immunosuppression caused by dexamethasone may be

the underlying mechanisms for the higher number of responders observed in the NovoTTF-100A cohort.

Future clinical trials on the NovoTTF-100A device must include stratification of potential predictive factors of response that include both genetic and epigenetic determinants. It is important to note that the genetic makeup of secondary glioblastomas is different from those of primary glioblastomas and these differences may determine whether or not a glioblastoma responds to a specific therapy. Therefore, genetic profiling of the tumor among patients enrolling into future NovoTTF-100A clinical trials would greatly facilitate the identification of those who are likely, as well as others who are unlikely, to respond to treatment. Furthermore, future trials may also need to include immune modulator that may augment the immunological effect of alternating electric fields. Such concerted approach to treatment will hopefully increase the response rate and efficacy of NovoTTF-100A against glioblastoma.

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## Conflict of Interest

ETW and KDS are currently conducting research funded by Novocure. ZR owns Novocure stock. ETW, HHE, ZR, and JLV serve in an advisory role for Novocure. The remaining authors have no conflicts of interest.

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# Health-related quality of life, cognitive screening, and functional status in a randomized phase III trial (EF-14) of tumor treating fields with temozolomide compared to temozolomide alone in newly diagnosed glioblastoma

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**Abstract** We characterized health-related quality of life (HRQoL), cognitive, and functional status in newly diagnosed glioblastoma (GBM) patients receiving Tumor treating fields (TTFields) with temozolomide (TMZ) versus TMZ alone in a planned interim analysis of a randomized phase III trial [NCT00916409], which showed significant improvement in progression-free and overall survival with TTFields/TMZ. After radiotherapy with concomitant TMZ, newly diagnosed GBM patients were randomized (2:1) to TTFields/TMZ (n = 210) or TMZ (n = 105). Interim analysis was performed in 315 patients with ≥18 months of

follow-up. HRQoL, a secondary endpoint, was evaluated in per-protocol patient population and expressed as change from baseline (CFB) at 3, 6, and 9 months for each subscale in the EORTC QLQ-C30/BN20. Karnofsky performance scores (KPS) and Mini-Mental State Examination scores (MMSE) were assessed. CFB in HRQoL was balanced in treatment groups at the 12-month time point. Initially, HRQoL improved in patients treated with TTFields/TMZ (CFB3: 24% and CFB6: 13%) versus TMZ (CFB3: −7% and CFB6: −17%), though this difference was no longer evident at the 9-month point. General scales, including physical and social functioning, showed no difference at 9 and 12 months. TTFields/TMZ group reported higher concerns of “itchy skin”. KPS over 12 months was just below 90 in both groups. Cognitive status (MMSE) was stable over time. HRQoL, KPS, and MMSE were balanced in both groups over time. There was no preliminary evidence that HRQoL, cognitive, and functional status is adversely affected by the continuous use of TTFields.

**Keywords** Glioblastoma · Health-related quality of life (HRQoL) · Cognition · Tumor treating fields · Temozolomide · EF-14

## Introduction

Glioblastoma (GBM) is the most aggressive and common malignant primary brain tumor in adults, with an estimated 9600 to 11,200 new cases diagnosed in the US yearly [1]. Patients with GBM have a poor prognosis with median overall survival (OS) of 14.6 months in clinical trial settings and 11 months in general GBM population [2, 3], and patients experience recurrence on average within 7 months despite use of multimodal therapies [3, 4]. Given that novel

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treatment approaches for GBM have only offered modest gains in OS and/or progression-free survival (PFS), their role in improving functioning or palliating adverse symptoms has been highlighted, and thus assessment of neurocognitive functioning (NCF) and health-related quality of life (HRQoL) has gained priority in neuro-oncology trials [5].

Quality of life is a multi-faceted construct, encompassing physical, emotional, cognitive, and social functioning, and characterized by patient self-report to reflect a subjective assessment of well-being [6]. In addition to self-report, objective assessment of cognition through validated measures is also recommended, as it has been shown to relate to patients' ability to perform basic and instrumental activities of daily living [7] and to have independent prognostic value for disease progression [8]. A large portion of patients with GBM experience reduced HRQoL, as well as decrement in objectively measured NCF in the pre-treatment setting [9]. Additional decline in HRQoL and NCF typically occurs throughout the course of the disease, secondary to side effects from therapies, tumor recurrence or progression, and disease related complications, such as seizures and venous thromboembolic events [6]. Therefore, measurement of HRQoL and NCF, as well as patient functional status via the Karnofsky Performance Score (KPS) at multiple time points have become standard in clinical trials for novel therapeutic approaches targeting glioma [5]. Furthermore, data regarding quality of life and cognition are factored into drug-efficacy metrics and can in turn inform physician and patient decision-making regarding choices of treatment [6].

Current standard-of-care treatment for newly diagnosed GBM includes maximum safe resection or biopsy and adjuvant concomitant radiation with temozolomide (TMZ) during the induction phase, followed by monthly TMZ for 6–12 months [3, 10]. Tumor Treating Fields (TTFields, Optune, Novocure, Ltd., Haifa, Israel) is a novel cancer therapy that leads to mitotic arrest and apoptosis of dividing cells by disrupting mitotic spindle formation during metaphase [11] and causing dielectrophoretic movement of polar molecules during cytokinesis [12]. The results from a randomized phase III trial (EF-11) comparing its efficacy with regard to extending OS and PFS in recurrent GBM in comparison to best physician chosen chemotherapy have been previously published [13]. Data from the trial indicated superior HRQoL for the TTFields group, pertaining to self-ratings of cognitive and emotional functioning in particular, as well as with regard to treatment related toxicity (appetite loss, constipation, diarrhea, nausea, and vomiting were more prevalent in the chemotherapy-treated arm). Most recently, a randomized phase III clinical trial (NCT00916409) for newly diagnosed GBM comparing TTFields/ TMZ versus TMZ alone has demonstrated superior outcomes of the treatment arm versus control arm in both OS and PFS at the pre-planned interim analysis time point [14]. This report focuses

on the findings detailing HRQoL, cognitive, and functional status in the same trial.

## Patients and methods

Full study details have been published previously [14]. Briefly, patients with newly diagnosed supratentorial GBM, age 18 and above, with KPS score of 70 or higher, with adequate bone marrow, liver, and renal functions were eligible for this trial. Patients were randomized at a ratio of 2:1 to receive TTFields/TMZ versus TMZ alone. Treatment with TTFields was initiated within 4–7 weeks from the last dose of the concomitant TMZ and radiation therapy. Randomization was performed through a central web-based randomization system and was stratified by extent of resection and O6-methyl guanine DNA methyltransferase (MGMT) gene methylation status. Raw scores on the HRQoL measures were normalized (range 0–100). A change of 10 points on a scale in either direction was regarded as the minimal clinically significant change [15].

Patients in the TTFields/TMZ group received continuous TTFields combined with cyclic TMZ per standard of care. TTFields was administered via placement of two pairs of transducer arrays on shaved scalp according to an individualized array map based on patient magnetic resonance imaging (MRI) and tumor location(s). The transducer array map was generated using mapping software designed for optimization of field intensity within the treated tumor (NovoTAL®, Novocure Ltd). The TTFields generate 200 kHz alternating electric fields within the brain. Following training in array placement, patients were supplied with transducer arrays in sterile packaging in order to replace arrays at home every 3 days. It was recommended that patients use the TTFields continuously to reach a goal of an average of 18 h per 24 h in a 4 week period; short treatment breaks were allowed. For those with tumor progression, second-line chemotherapy was offered per choice of the treating physician. In the TTFields/TMZ group, TTFields could be maintained until a second radiological progression or a maximum of 24 months. The study was approved by institutional review boards of all 83 participating institutions. All patients had reviewed and signed informed consent prior to enrollment in the study.

## Procedures

At baseline, in addition to undergoing contrast-enhanced MRI of the brain (within 2 weeks prior to the start of treatment), comprehensive assessments were performed (within 1 week of treatment initiation) including physical and neurological examinations, collection of laboratory parameters, and measurement of patient independence in



activities of daily living with the KPS. Patients completed questionnaires assessing HRQoL and cognitive screening with the Mini-Mental Status Exam (MMSE) [16]. HRQoL was assessed with an EORTC quality-of-life questionnaire core-30 (QLQ-C30, Version 3), supplemented by the brain cancer module (BN20). Thereafter, MMSE and KPS assessments were repeated once monthly during office visits, and the HRQoL questionnaires were administered once every 3 months until progression or withdrawal from the trial.

The EORTC quality of life questionnaire C30 (EORTC QLQ-C30) is a general 30-item core measure used in many multi-national clinical trials with cancer patients [6] and is supplemented by the EORTC QLQ Brain Neoplasm 20 (BN20), which was developed specifically for patients with brain cancer. Robust reliability and validity have been established for both measures [17, 18]. Subscales within the EORTC QLQ-C30 include: (a) five functional scales—physical, role, emotional, cognitive, and social, as well as a global health status rating; (b) three symptoms scales—nausea, vomiting, and fatigue; and (c) six single-item scales—insomnia, appetite loss, constipation, diarrhea, dyspnea, and financial effect of tumor/treatment. The BN20 comprises four domain scores: visual disorder, motor dysfunction, communication deficit, and future uncertainty, and seven individual symptom items: seizures, difficulty with bladder control, weakness in legs, headache, drowsiness, hair loss, and itching. All measures were scored in accordance with the recommended standardized approach [19]. For the EORTC QLQ-C30, a higher positive score on a functional scale or on the global health status scale represents improved functioning, whereas higher scores on symptom scales and single item scales represent a high level of symptomatology/difficulty.

The MMSE is a brief cognitive screening measure that has been translated into multiple languages and is designed to sample orientation (place and time), registration, attention, recall, language, and visual construction with a maximum total score of 30 points [20]. It has been shown to have acceptable reliability and validity in patients with dementia, though lower reliability values have been recorded in relatively “healthy” community samples [20]. A cut-off of 27 points was chosen to discriminate between cognitively impaired versus cognitively intact participants in accordance with findings among individuals of Caucasian background with higher levels of education [21].

Prospective recording of adverse events was implemented in accordance with the National Cancer Institute’s Common Terminology Criteria (version 3.0) and began from initiation of treatment of either TTF/TMZ or TMZ alone until 2 months after discontinuation of treatment. The descriptive interim findings with regard to presence of adverse events in each study group have been reported previously [14].

Given that cognitive status, functional status, and health-related quality of life were secondary endpoints of the EF-14 trial, analysis was performed on the per protocol patient population: TTFields/TMZ (n = 196) and TMZ alone (n = 84). Descriptive data was expressed as change from baseline (CFB), which was calculated for each time point over the course of the first year post-randomization, and is presented in the “Results” section.

## Results

A total of 695 patients diagnosed with supratentorial GBM were randomized (2:1 ratio) to receive either TTFields/TMZ or TMZ alone between July 2009 and November 2014. As pre-specified, the interim analysis was performed when 210 and 105 patients were randomized to the TTFields/TMZ and TMZ alone, respectively, with a median follow-up of 38 months (range 18–60 months) (Fig. 1). The median time from randomization to treatment was 37 days (from the last day of radiotherapy to randomization). As the pre-defined boundaries for trial success (improvement of both PFS and OS) were met, the independent data and safety monitoring committee at the October 2014 meeting recommended termination of the study. The US Food and Drug Administration approved study termination; recruitment closed on November 29, 2014, when 695 of the planned 700 patients were enrolled. Patients in the TMZ alone arm were allowed to cross over to receive TTFields and follow-up of all patients continued in accordance with study protocol.

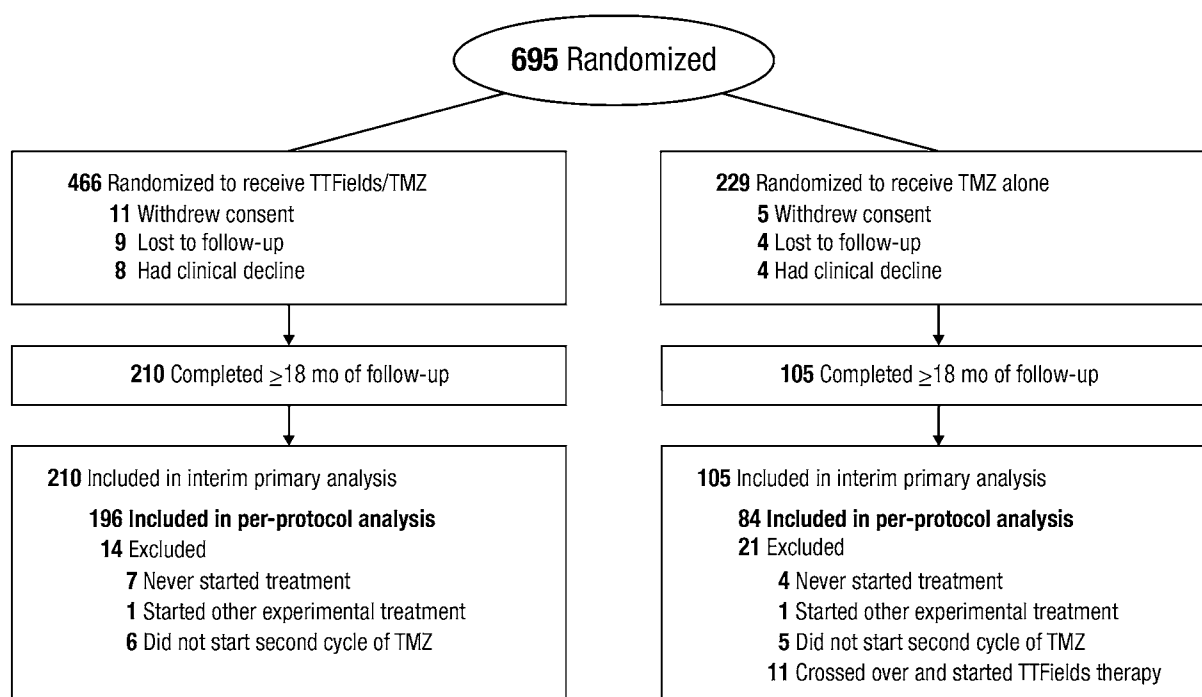
Patient baseline characteristics at interim analysis were well balanced between the two treatment groups (Table 1) [14]. Median age was 57 years and 66% were male. Tumor location was similar across groups. A gross total resection was achieved for 64% of the participants in each group, whereas about 11% had a biopsy in each arm. Use of anti-epileptic medication and corticosteroid therapy was comparable across the two groups. Median KPS score at baseline was 90 for each group. Based on MMSE scores at baseline, 15 and 13% were classified as cognitively impaired at baseline in the TTFields/TMZ and TMZ groups, respectively.

HRQoL assessment was a secondary endpoint of the study and was analyzed in the per protocol population. Compliance with questionnaire (EORTC QLQ-C30 and BN20) completion was 82% (173/210) in the TTFields/TMZ group and 64% (67/105) in the TMZ alone group. All assessments were carried out until the number of remaining patients was  $\leq 70$ .

### Functional and cognitive status

KPS ratings at baseline and monthly thereafter reflected relative stability with regard to patient independence in activities



**Fig. 1** Patient flow**Table 1** Baseline characteristics (per protocol population)

Baseline characteristics	TTFields/TMZ (n = 196) n (% or range)	TMZ (n = 84) n (% or range)
Age: median (range)	57 (20–83)	58 (21–80)
Sex: M/F	133/63 (67.9/32.1)	54/30 (64.3/35.7)
KPS: median (range)	90 (60–90)	90 (70–100)
Time from diagnosis to randomization (days)	116 (59–171)	113 (43–170)
Tumor location		
Both	2 (1.0)	1 (1.2)
Corpus Callosum	8 (4.1)	3 (3.6)
Left	87 (44.4)	32 (38.1)
Right	99 (50.5)	48 (57.1)
Extent of resection		
Biopsy	21 (10.7)	10 (11.9)
Gross total resection	127 (64.8)	54 (64.3)
Partial resection	48 (24.5)	20 (23.8)
Cycles of TMZ (Median and range)	6 (1–26)	4 (1–24)
Cycles of TTFields	9 (1–58)	0 (0)

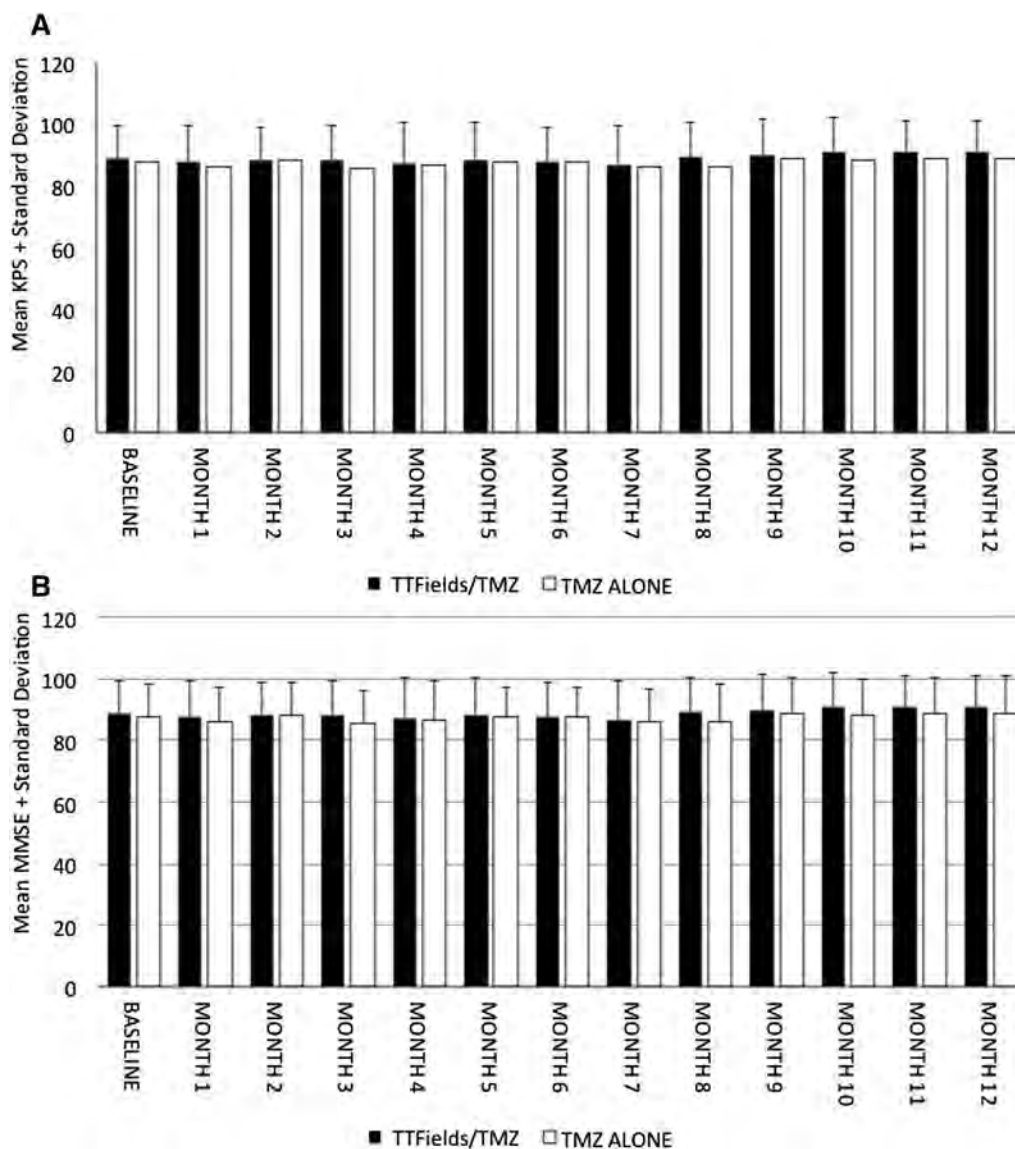
of daily living over time during the first year after randomization in either group; the majority of mean scores remained just under 90 (Fig. 2a). Mean percentage change from baseline (CFB) was between −4.3 (month 7) and −1.6 (month 1) within the TTFields/TMZ group and between −4.2 (month

8) and −0.4 (month 2) in the TMZ alone group. Similarly, mean cognitive status within either group did not decline below 27/30 and no differences in MMSE scores were documented between the groups (Fig. 2b). Mean percentage change in MMSE scores ranged from −2.4 (month 1) to 4.8 (month 8) in the TTFields/TMZ arm, and from −0.5 (month 2) to 3.8 (month 8) in the TMZ alone group.

### Health-related quality of life (HRQoL)

At 3 and 6 months, HRQoL initially improved in patients treated with TTFields/TMZ (CFB3: 24% and CFB6: 13%) versus mild reduction in the TMZ group (CFB3: −7% and CFB6: −17%). However, at 9 months the CFB were 0.42 (2.9%) in the TTFields/TMZ group, and 0.0 (7.8%) in the TMZ group (Fig. 3). There were no significant changes registered from baseline values on any of the quality-of-life scales (Fig. 4). No significant group differences were reported for any of the functional scales from the EORTC QLQ-C30 measure. Patients did not rate their physical or social functioning any differently when receiving TTFields/TMZ versus TMZ alone. Group differences were pronounced for “itchy skin,” where patients receiving TTFields/TMZ had higher numeric scores (Fig. 5). Self-reported neurologic symptomatology on BN20 did not differ between the two groups and as expected reflected a tendency toward increase in symptoms, likely related to known side effects of TMZ, which was administered to both groups.





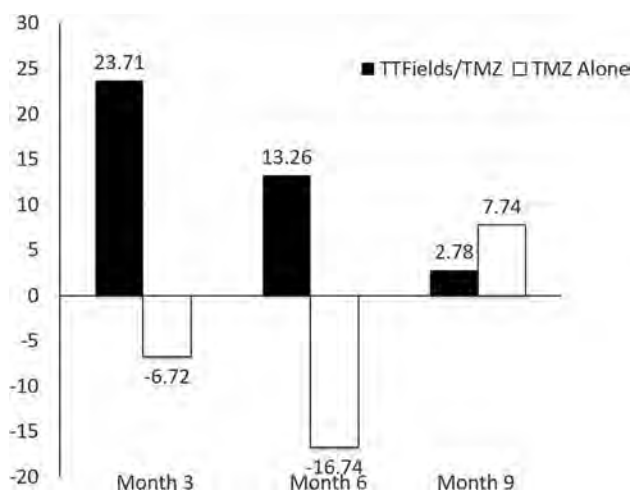
**Fig. 2** Mean changes in KPS (a) and MMSE (b) over 12 months with TTFields/TMZ versus TMZ alone. (Per Protocol Population)

## Discussion

The current study reviewed available data at the interim analysis from the first multicenter international phase III clinical trial of TTFields added to standard-of-care therapies in patients with newly diagnosed glioblastoma (EF-14). Although findings characterizing the efficacy of TTFields with regard to OS and PFS have been encouraging and were published elsewhere [14], this is the first report of cognitive status, self-reported HRQoL and performance status at the pre-planned interim analysis of the trial. As such, the data presented herein may offer important implications for the provision of clinical care to individuals with newly diagnosed glioblastoma and their families and highlights directions for future study.

Interim review of the data revealed no significant group differences across any of the administered measures, including mean cognitive status, KPS-assessed functional status, and HRQoL. Results indicated that patients receiving TTFields/TMZ and TMZ alone, on average, had intact cognitive status (all means stayed above the 27-point cut-off for both groups) and were independent with regard to functional status (KPS mean scores at 3, 6, 9, and 12 months following randomization remained just below 90). Mean self-reported functional scales from the EORTC QLQ-C30 did not differ between the two groups, including self-ratings of social functioning and physical functioning, which could theoretically be adversely impacted by wearing the TTFields device. Findings from the cognitive screening (MMSE) showing no adverse change in cognitive status were congruent with





**Fig. 3** Changes from baseline (%) in Global Health Status from baseline to 9 months with TTFields/TMZ versus TMZ alone. (Per Protocol Population). An increase in percentage corresponds to an increase in QoL

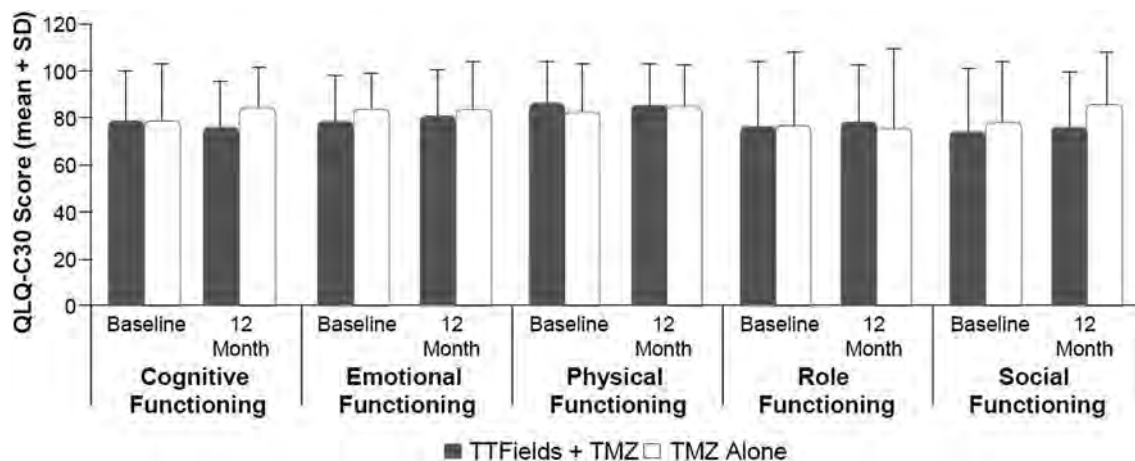
results from HRQoL measures revealing no significant CFB in self-ratings of cognitive functioning. Similarly, self-reported emotional functioning was also not significantly different relative to baseline in both groups at months 3, 6, and 9. Although symptoms known to be associated with TMZ treatment (e.g., nausea/vomiting, diarrhea, constipation, appetite loss, fatigue and pain) were reported by both groups, no differences were noted between treatment groups.

The present HRQoL findings are consistent with results from the previous phase III trial (EF-11) assessing efficacy and HRQoL in patients with recurrent GBM treated with TTFields versus physician best choice chemotherapy [13]. Similarly, there were no differences between the TTFields

group and patients receiving chemotherapy on self-ratings of global health and social functioning; ratings of cognitive and emotional functioning were higher in the TTFields group, and role functioning favored TTFields. In addition, pain and fatigue were increased only in the chemotherapy patients, but not in the patients receiving TTFields.

Limitations inherent in the design of the current clinical trial have been addressed elsewhere and comprise: exclusion of patients with very poor prognoses due to the timing of randomization; reporting bias given that patients in the TTFields group were allowed to remain in the trial beyond progression; and absence of a sham/placebo treatment [14]. Compliance with questionnaire (EORTC QLQ-C30 and BN20) completion was 82% (173/210) in the TTFields/TMZ group and 64% (67/105) in the TMZ alone group due to more patients in the TMZ arm withdrawing consent after GBM progression to participate in other trials, whereas patients in the TTFields/TMZ arm continued treatment and clinical follow up with MMSE and KPS collected monthly during office visits, and HRQoL questionnaires completed every 3 months until a second progression. It can be extrapolated that missing data from noncompliant participants in the TMZ group would likely skew toward poorer ratings for HRQoL and reduced cognitive status, given findings of declining functioning with advancement of disease. Nevertheless, increased efforts to collect HRQoL data, and perform cognitive screening and assessment of functional status as participants exit the trial, in addition to the measurements collected at assigned study time intervals, are recommended in order to provide more complete comparisons between treatment modalities.

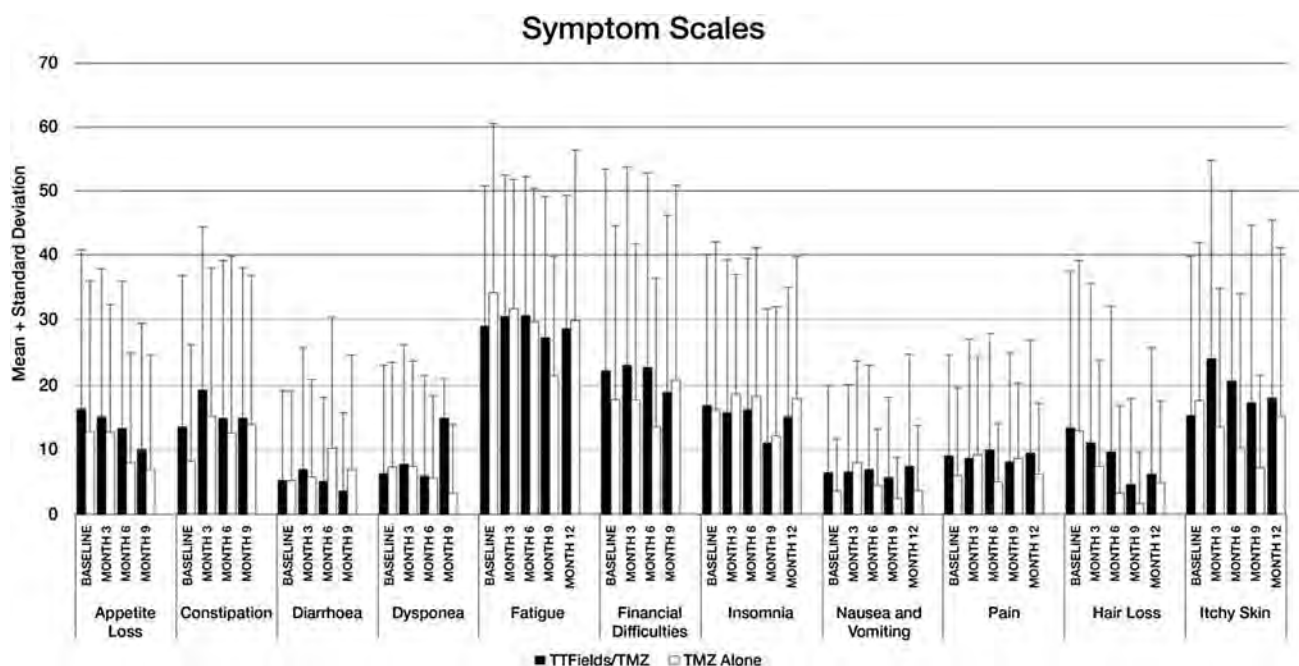
The use of the MMSE to measure cognition in clinical trials of patients with primary brain tumor has been questioned on grounds of poor sensitivity, potential practice effects with



**Fig. 4** QLQ-C30 Global Health Status and General Scales in TTFields/TMZ versus TMZ alone groups over 12 months in Per Protocol Population. EORTC QLQ-C30, European Organisation for

Research and Treatment of Cancer Quality of Life Questionnaire-C30; SD standard deviation, TMZ temozolomide, QoL quality of life





**Fig. 5** QLQ-C30 Symptom Scales in TTFIELDS/TMZ versus TMZ alone groups over 12 months in Per Protocol Population. An increase in percentage corresponds to a decrease in QoL

repeated administration, and the failure to adequately sample frontal subcortical functions impacted by radiotherapy [22]. Brevity, low cost, and ease of administration during a typical office visit has contributed to wide utilization of MMSE in multiple phase II and phase III clinical trials. It is noted that, had the current study utilized neurocognitive measures with higher sensitivity, as has been suggested in other work [23, 24], greater decline from baseline in cognition may have been documented in both treatment groups, consistent with levels registered in other investigations. The MMSE has been demonstrated to capture cognitive status deterioration in patients receiving escalating doses of radiation [23], hypofractionated radiation with TMZ [24], as well as in patients experiencing first progression of GBM while enrolled in a bevacizumab plus standard-of-care clinical trial [25]. MMSE scores have also been shown to correlate to scales assessing activities of daily living [25]. Nevertheless, given the demonstrated feasibility of more sensitive neurocognitive measures and explicit recommendations by the International Cognition and Cancer Task Force [26], further investigation of potential neurocognitive impact of TTFIELDS on patients with GBM is warranted in future studies. In addition, in light of the high KPS and MMSE scores recorded in both treatment groups in the present study, future investigations in patients with GBM where cognitive deficits may range from very subtle to severe are cautioned to exercise care in employing neurocognitive tests with demonstrated sensitivity to milder decline in cognitive and performance status.

In summary, prospective measurement of HRQoL and neurocognitive functioning as part of clinical trials evaluating novel treatments for GBM has become standard in recent years. It is critical to adequately monitor treatment-related cytotoxicity and provide a multifaceted assessment of the impact of the illness and treatments on patient daily functioning, particularly in light of the limited survival duration for these individuals. As further advances are made in the GBM treatment arena, such data would be essential in providing guidelines regarding expected side effects and informing physician and patient choices of preferred treatment modality.

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**Compliance with ethical standards**

**Conflict of interest** Jay-Jiguang Zhu, MD, PhD has disclosed that he has received research funding from Novocure Inc., Five PRIME, Inc. Immuno-Cellular Inc., Diffusion Pharmaceuticals LLC, and DEKTEK, Inc. Petya Demireva, PhD, declares that she has no conflict of interest. Andrew Kanner, MD, declares that he has no conflict of interest. Susan Pannullo, MD, declares she has served as a consultant or participated in an advisory board for Cancer Panels, Guidepoint Global, Clearview Healthcare Partners, ICF International and MAPI; has received research funding from Novocure, Celldex, Immunocel-



lular Therapeutics, and Stemline, and holds a patent from Arrow Development Corp; and has received reimbursement for travel from Cancer Panels. Maximilian Mehdorn, MD, has declared he served as a consultant or participated in an advisory board for Stryker Leibinger. Nicholas Avgeropoulos, MD, has declared he received honoraria from and participated in a speakers bureau for Novocure. Andrea Salmaggi, MD, has provided expert testimony from UCB and has received travel reimbursement from Italfarmaco. Antonio Silvani, MD, has declared he received honoraria and research funding from Novocure. Samuel Goldlust, MD, declares that he has no conflict of interest. Carlos David, MD, declares he owns stock in Kogent Surgical. Alexandra Benouaich-Amiel, MD, declares receiving research funding from Roche. Zvi Ram, MD, has declared owning stock in Novocure and receiving honoraria from Novocure and Research to Practice Meeting, and has received travel reimbursement from Novocure, BrainLAB, and Electra Pharmaceuticals.

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# Tumor Treating Fields

Laura Benson

This chapter provides an understanding of the science of Tumor Treating Fields (TTFields), an innovative antimitotic therapy used to treat solid tumors. The mechanism of action, the delivery system, and the use of TTFields are addressed, as are the prevention and management of side effects and the importance of patient adherence to optimize outcomes when using this therapeutic device.

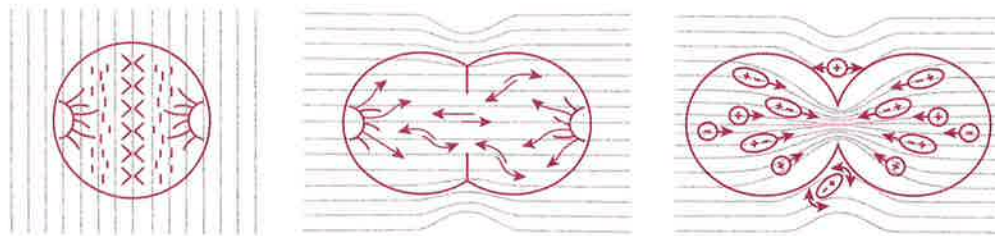
## Definition of TTFields

TTFields are low-intensity alternating electric fields within the intermediate frequency range. TTFields disrupt cell division through physical interactions with key molecules during mitosis. This mechanism is grounded in the properties of physics that exploit the inherent attributes of cellular components (Kirson et al., 2004). Specifically, TTFields take advantage of the electrical characteristics, geometrical shape, and replication rate of dividing cancer cells, all of which make them susceptible to the effects of frequency-tuned alternating electric fields. TTFields therapy is unlike any other previous applications of electricity in medicine. TTFields therapy does not deliver electric current to tissue, stimulate nerves or muscles, or heat tissue (Kirson et al., 2009).

## Mechanism of Action

TTFields exert an anticancer effect through a multipronged mechanism of action. TTFields therapy creates an alternating electric field within the tumor that attracts and repels the charged components of the cells during mitosis at intermediate frequencies of 100 to 300 kHz and at an intensity of approximately 1 V/cm, TTFields. This alternating field acts at multiple phases of the cell cycle (see figure below):

- It disrupts normal mitotic spindle assembly during metaphase, which leads to mitotic arrest and subsequent apoptosis (Giladi et al., 2014a).
- It produces nonuniform electric fields within dividing cells that exerts a force known as *dielectrophoresis*. This force within the electric fields affects intracellular components such as organelles and macromolecules. During mitosis, the effect of dielectrophoresis pushes the cell parts toward the cell cleavage furrow and interferes with normal cell division cytokinesis.
- It disrupts normal cell division, causing abnormal chromosomal segregation and multinucleation and thereby reducing the clonogenic potential in cellular progeny (see figure below).

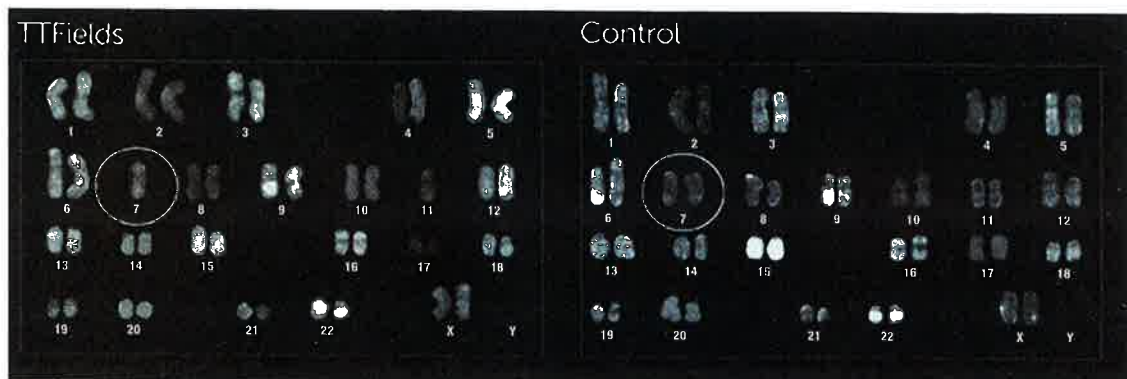


Metaphase

Anaphase

Telophase

**Mechanism of action of TTFields.** (© 2015 Novocure. All rights reserved.)



**TTFields impair normal cell nuclear division.** This causes abnormal chromosomal segregation (example showing abnormalities in chromosome 7). (© 2015 Novocure. All rights reserved.)



- It induces mitotic catastrophe (i.e., a major cell disruption during mitosis), which eventually leads to apoptotic cell death.
- It induces endoplasmic reticulum (ER) stress pathways and increases the expression of proteins known to activate immunogenic cell death.
- It impair a cell's ability to repair DNA damage caused by exposure to radiation.

TTFields therapy is a regional anticancer modality with no half-life or impediment posed by the blood-brain barrier, thus sparing off-target systemic adverse effects. TTFields are frequency tuned to exert a maximal cytotoxic effect on specific cancer cell types, sparing normal healthy cells. Different cell lines exhibit maximal proliferation reduction at different frequencies (Kirson et al., 2007). For example, glioma cells exhibit the greatest reduction in proliferation at a frequency of 200 kHz (Kirson et al., 2007), whereas for non-small cell lung cancer (NSCLC) cells, the greatest reduction in cell proliferation is at 150 kHz (see table below) (Giladi et al., 2014b). Efficacy is dose dependent; cytotoxic effects increase when the electric field intensity increases. Threshold value, below which cells are largely unaffected, is approximately 1 V/cm. Unlike drug therapy, TTFields deliver therapy only while activated.

### Efficacy of TTFields Is Frequency Dependent

Tumor Cell Line	TTFields Frequency for Greatest Reduction in Cell Proliferation (kHz)
Glioma	200
Meningioma	200
Non-small cell lung cancer	150
Ovarian	200
Pancreatic	150

From Benson, L. (2015). Technology meets oncology: Understanding the science of tumor treating fields, a novel antimitotic therapy for solid tumors. Presented at the Oncology Nursing Society 40th Annual Congress, April 23-26, Orlando, Florida. Poster session #35. *Oncology Nursing Forum*, 42(2), E154; Davies, A. M., Weinberg, U., Palti, Y. (2013). Tumor treating fields: A new frontier in cancer therapy. *Annals of the New York Academy of Sciences*, 1291, 86-95.

### TTFields Therapy System

Optune (Novocure Inc., Portsmouth, NH), formerly called the NovoTTF-100A System, is a medical device approved in the United States and Japan for use as monotherapy for the treatment of recurrent glioblastoma (GBM). Optune is a CE Marked device that is cleared for sale in the European Union, Switzerland, Australia, and Israel for glioblastoma and NSCLC. The complete TTFields therapy delivery system includes an electric field generator; insulated transducer arrays; portable, rechargeable batteries; battery charger; plug-in power supply; connection cable; and carrying case (see figure in next column) (Optune, 2014). Ongoing therapy is patient administered in the home after prescription by a certified health care provider. The U.S. Food and Drug Administration (FDA) mandates that prescribers of

this therapy successfully complete a certification course provided by the manufacturer. The patient is monitored in the outpatient setting by the oncology team on a regular basis. During the course of therapy, patients receive replacement system parts, most often the transducer arrays, from the manufacturer. When the therapy is discontinued, the system is returned to the manufacturer.



Optune medical device. (© 2016 Novocure. All rights reserved.)

Cell response to TTFields is direction dependent. The cells that divide parallel to the electric field show higher rates of damage than those dividing perpendicular to the field (Kirson et al., 2004). Therefore, to maximize the clinical effects, TTFields are delivered noninvasively via two pairs of transducer arrays that produce two perpendicular electric fields. These arrays are applied directly on the surface of the skin in the region surrounding the tumor. TTFields are frequency-tuned to the targeted histology, and during treatment, generation of the electric field switches between the two pairs of arrays at a rate of approximately once per second.

Each array comprises nine insulated ceramic discs (see lower left part of figure on page 172) which have a high dielectric constant, are biocompatible, and are soldered to a flexible circuit board. These discs are separated from the skin by a layer of conductive hydrogel. To keep the arrays in place on the scalp and in continuous direct contact with the skin, the ceramic discs, hydrogel, and circuitry are attached to a hypoallergenic medical adhesive bandage (Lacouture et al., 2014). TTFields therapy should not be used in patients with GBM who have an active implanted medical device, a skull defect, or bullet fragments (Optune, 2014).

A wire from each array plugs into the connection cable, which then plugs into the portion of the device that generates TTFields. Patients may describe a "warm sensation" under the transducer arrays. Each array has eight temperature sensors that monitor temperature; the device will shut off and sound an alarm if array temperature exceeds 41° C (105.8° F), well below the threshold for a thermal skin burn (Lacouture et al., 2014).



In patients with GBM, transducer array placement is based on the results of magnetic resonance imaging. The array locations on a patient's shaved scalp are calculated with the use of FDA-approved simulation software (NovoTAL, Novocure) that optimizes field intensity within the tumor, based on head size and tumor location (see figure below) (Lacouture et al., 2014). Treatment parameters are preset at 200 kHz and a minimal field intensity of 0.7 V/cm in the brain. Neither the health care provider nor the patient needs to make electrical adjustments (Lacouture et al., 2014). Responses to TTFields therapy are typically observed on radiographic evaluations 3 to 5 months after treatment initiation (Vymazal et al., 2014).



Transducer array placement is guided by a patient's MRI results. (© 2016 Novocure. All rights reserved.)

### TTFields Therapy for Recurrent Glioblastoma

In 2011, TTFields therapy was approved by the FDA for use in adults (22 years of age or older) who have recurrent GBM in the supratentorial region of the brain after receiving chemotherapy and whose disease is refractory to surgical and radiation treatment options. The pivotal phase III trial that led to FDA approval in recurrent GBM demonstrated comparable median overall survival time with TTFields therapy compared with chemotherapy, including bevacizumab (Stupp et al., 2012). TTFields therapy was found to be as effective as chemotherapy, with fewer side effects. In addition, patients reported a better quality of life, including improved cognitive and emotional functioning, compared with patients receiving chemotherapy (Stupp et al., 2012). Treatment adherence, or time on therapy, has proved to be an important factor in treatment outcomes. Analysis of the pivotal phase III trial for recurrent GBM showed that an adherence rate of at least 75%, or approximately 18 hours/day, was a clear predictor of survival (Gutin & Wong, 2012; Mrugala et al., 2014; Optune, 2014).

In the Patient Registry Dataset (PRiDe), a postmarketing registry of all commercially treated patients with recurrent GBM receiving TTFields, median overall survival significantly exceeded that observed in the pivotal trial. Favorable

prognostic factors included use in first recurrence, no prior exposure to bevacizumab, and high performance status (Mrugala et al., 2014).

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Central Nervous System Cancers indicate that physicians should consider TTFields therapy for patients with GBM who experience recurrence or progression after initial treatment (category 2B) (NCCN, 2015).

### Newly Diagnosed GBM

When combined with temozolomide in human glioma cell line studies, TTFields were found to exert additive cytotoxic effects. This provided the rationale for a phase III trial in patients with newly diagnosed GBM who had completed standard-of-care concomitant chemoradiotherapy. Patients were randomly assigned in a 2:1 ratio to receive either adjuvant temozolomide chemotherapy alone or temozolomide in combination with TTFields therapy (200 kHz). The primary end point was progression-free survival; secondary end points were overall survival, safety, cognitive function, and quality of life. Based on a prespecified interim analysis of 315 patients, the trial was closed early. The first analysis of the full dataset of 700 patients randomized in the trial found progression-free survival to be 7.1 months for the combined therapy versus 4.0 months for temozolomide alone. Overall survival was 20.5 versus 15.6 months, respectively. This translated into 2-year survival rates of 43% for combined therapy with temozolomide and TTFields, compared with 29% for temozolomide alone. No significant added toxicity was observed with the addition of TTFields. Quality of life and gross cognitive function were comparable in both study arms (Stupp et al., 2014; Stupp et al., 2015). Based on these results U.S. FDA has approved Optune in combination with temozolomide for the treatment of adult patients with newly diagnosed GBM.

### Patient and Caregiver Education Before TTFields Therapy

Because TTFields is a continuous, at-home therapy, patient and caregiver education is important. Patients and caregivers should have a basic understanding of the mechanism of action, the system parts and functions, proper use of the equipment, and the importance of compliance with therapy. TTFields therapy is delivered only when the system is in place and activated; therefore, the device is portable and designed to be worn continuously, around the clock. Patient adherence is critical because greater time on therapy is linked to better outcomes (Mrugala et al., 2014). Therefore, patient teaching, ongoing assessments, and continued motivation of patients and their caregivers are key to maximizing the potential benefits received from TTFields therapy. Education on skin preparation and care, prevention and management of side effects, and what to expect during treatment is essential.



### Patient Teaching

Patients should use TTFields only after being trained by qualified personnel who have completed a training course (Optune, 2014). This includes instruction about caring for the system components, how best to prevent and manage skin irritation, and the importance of treatment adherence.

It is important for the family to understand that electric field therapy is not hazardous to those in close proximity to the patient. The electric fields do not contain radiation or pose a hazard to others.

Patients are instructed to remove the transducer array portion of the system every 4 to 7 days to re-shave the head and reapply the transducer arrays. The four transducer arrays that are placed on the scalp need to be replaced every 4 to 7 days and are for single use only. Used system parts (e.g., transducer arrays) are returned to the manufacturer for disposal. Practical tips on how to complete activities of daily living are taught. For example, the patient is taught how to shower without removing the transducer arrays by using a shower cap for bathing.

The delivery system is portable, allowing patients to go about their daily activities while receiving treatment (see figure below). Patients can spend time with family, work, travel, and generally engage in their usual activities, including showering or bathing.



Simulation of patient receiving TTFields therapy for GBM. (© 2016 Novocure. All rights reserved.)

Because treatment is delivered via a visible, constantly present device, support and dedication by both the patient and caregiver are critical to a successful outcome. The transducer

arrays must be changed one or two times per week (i.e., every 4 to 7 days). The time between changes varies based on factors such as sweating, hair growth, and weather. The patient and caregiver are taught this procedure at the start of therapy.

### Side-Effect Profile

Device-related adverse events can impact a patient's quality of life, affect adherence to therapy, and contribute to medical costs (Lacouture et al., 2014). The most commonly occurring adverse event associated with the use of TTFields therapy is skin irritation, largely grade 2 (mild to moderate), under the transducer arrays (see figure below). The types and potential causes of dermatologic adverse events are summarized in the table below, and the signs of skin events based on underlying pathogenesis in the table on page 176.

Prophylactic strategies to prevent skin irritation include proper shaving with an electric razor and avoiding the placement of ceramic discs directly over postsurgical screws or plates (Lacouture et al., 2014). Patients are taught how to properly shave and how to adjust the placement of the transducer arrays; they are advised to assess skin condition every 4 to 7 days. The table on page 176 highlights what the patient and caregiver can do to prevent dermatologic adverse events.



**Skin irritation.** Dermatologic erosions and skin infection (folliculitis) in a 60-year-old man who had been receiving temozolomide and NovoTTF Therapy for 3 months. (© 2016 Novocure. All rights reserved.)

### Types and Potential Causes of Dermatologic Adverse Events

Adverse Event	Potential Cause
Irritant contact dermatitis	Chemical irritation from hydrogel, moisture, alcohol
Allergic contact dermatitis	Allergy to tape, hydrogel
Erosion	Mechanical trauma from shaving, array pressure/removal
Ulcer	Decreased perfusion from array pressure (especially in areas overlying scars, hardware, or prior radiation fields)
Skin infection/pustules	Secondary bacterial infection

From Lacouture, M. E., Davis, M. E., Elzinga, G., Butowski, N., Tran, D., Villano, J. L., et al (2014). Characterization and management of dermatologic adverse events with the NovoTTF-100A System, a novel anti-mitotic electric field device for the treatment of recurrent glioblastoma. *Seminars in Oncology*, 41(Suppl 4), S1-S14.



## Signs of Skin Events Based on Underlying Pathogenesis

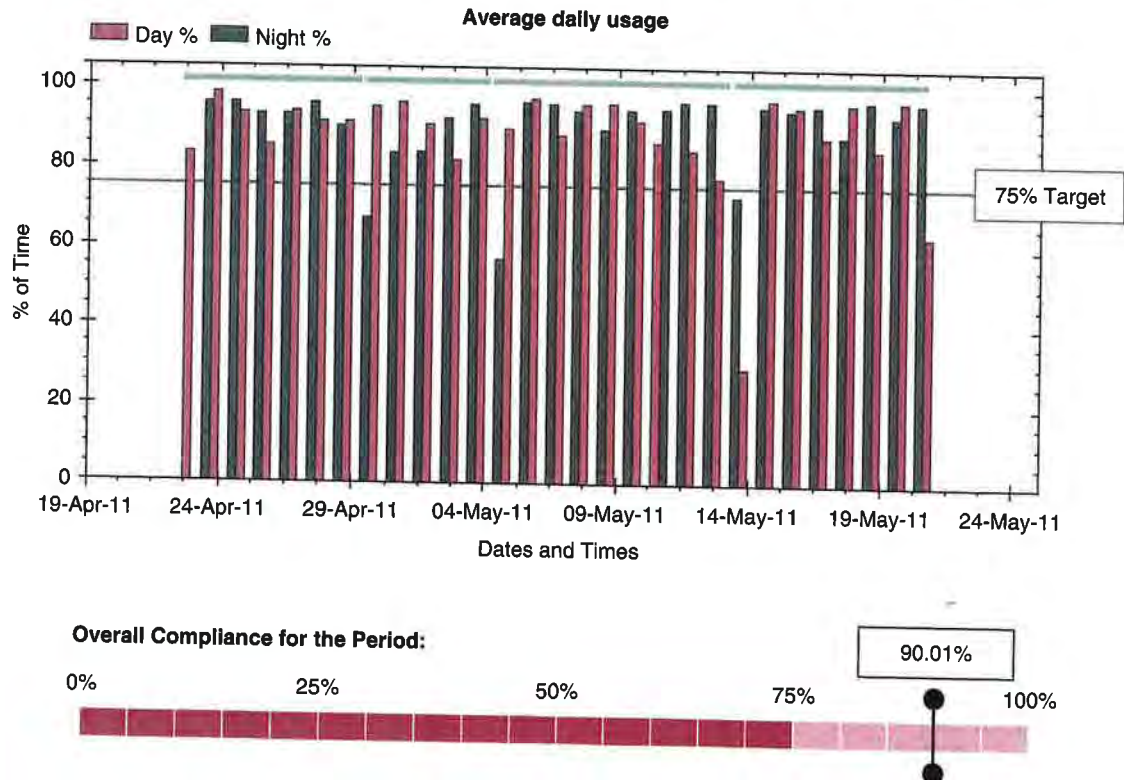
Dermatitis	Skin Infection	Mechanical	Ischemia
Erythema Scaling Erosions Edema Pruritus	Erythema Discharge Pustules Pain Yellow/green crusting	Erosions Abrasions Lacerations Pain/burning	Ulcers Pain

From Lacouture, M. E., Davis, M. E., Elzinga, G., Butowski, N., Tran, D., Villano, J. L., et al (2014). Characterization and management of dermatologic adverse events with the NovoTTF-100A System, a novel anti-mitotic electric field device for the treatment of recurrent glioblastoma. *Seminars in Oncology*, 41(Suppl 4), S1-S14.

## Preventive Strategies for Dermatologic Adverse Events

Category	Guidelines for Patient or Caregiver
Shaving and preparation of the scalp	Perform proper handwashing before preparation of the scalp for array application. Take time shaving the scalp, using gentle but firm circular motions. Ensure a close shave before applying the arrays. Cleaning the electric razor <i>after</i> every shave is important to lessen the risk of skin infection. Wash scalp with fragrance-free, mild shampoo (e.g., baby shampoo); seborrheic dermatitis shampoo may be used because it has antibacterial properties (e.g., pyrithione zinc 2%, ciclopirox 1%, ketoconazole 2%) Ensure that scalp is completely dry before applying a new set of arrays.
Use of 70% isopropyl alcohol	Use of first aid antiseptic rubbing alcohol before array application is a necessary step to remove naturally occurring scalp oils, resulting in better adherence of the arrays to the scalp. After shaving and before placing the arrays, wipe the scalp with a gauze or cotton ball soaked in the rubbing alcohol.
Transducer array exchanges	Avoid areas of skin irritation, because the rubbing alcohol may further irritate the skin. Change arrays on a regular basis (at least every 3-4 days). When removing the arrays, avoid "pulling" on the skin; take approximately 60 sec to remove each array. Use of mineral (baby) oil on the edges of the array may make removal of the adhesive tape easier and less irritating to the skin. To remove leftover array adhesive, use gauze or a cotton ball soaked in mineral (baby) oil or pour oil into hands and gently rub scalp in areas of remaining adhesive. Pay close attention to the scalp at each array exchange, and notify the doctor or nurse if there are signs of skin irritation or open areas, to receive information on how to treat them; taking a picture of the affected areas on the scalp and sharing it with the doctor or nurse is advised.

From Lacouture, M. E., Davis, M. E., Elzinga, G., Butowski, N., Tran, D., Villano, J. L., et al (2014). Characterization and management of dermatologic adverse events with the NovoTTF-100A System, a novel anti-mitotic electric field device for the treatment of recurrent glioblastoma. *Seminars in Oncology*, 41(Suppl 4), S1-S14.



Sample of a patient-specific adherence report. (© 2016 Novocure. All rights reserved.)



Specific treatments for dermatologic adverse events may include topical or oral antibiotics, topical corticosteroids (high potency as needed), and isolation of the affected skin areas from adhesives and pressure. If patients have intolerable grade 2 or 3 dermatologic adverse events, treatment should be interrupted and topical therapies applied. When the arrays are reapplied, they may be relocated (Lacouture et al., 2014). Other side effects reported by patients include headaches, weakness, falls, fatigue, and muscle twitching (Optune, 2014).

### Adherence

Patient adherence is recorded by the device onto internal log files. A patient-specific report is generated monthly and provided to the treating health care team (see figure on page 176) (Greifzu, Kuchinka, DiMeglio, Shackelford, & Benson, 2015). Patients may take short treatment breaks of 1 to 2 hours for personal care activities but are otherwise encouraged to continue normal activities of daily living while on therapy. Adherence can be maximized by having patients and caregivers adopt skin care strategies described in the previous section, minimizing the need for any treatment breaks. Use of properly ventilated hats and wigs may also improve adherence to TTFields therapy (Greifzu et al., 2015). Tightly woven wigs and hats made of material that traps heat can cause the device to alarm. The use of lighter materials, such as loosely woven wigs or ventilated wigs, permits heat to escape while providing a cosmetic effect.

### Ongoing Research with TTFields

A substantial body of evidence exists that supports the anticancer activity of TTFields across multiple cancer cell lines—including glioma, small cell lung cancer, breast cancer, melanoma, NSCLC, ovarian cancer, and pancreatic cancer—as well as in multiple animal tumor models and in patients with a variety of solid tumors. TTFields therapy has safely been combined with chemotherapy in clinical trials (Munster et al., 2015; Pless, Droege, von Moos, Salzberg, & Betticher, 2013).

### Additional Information

Optune is classified as durable medical equipment and it is approved for use within the home without continuous medical supervision. The therapy is covered by most major insurance carriers, either through published medical policy or on case-by-case review. Patient coinsurance varies by plan, and patients who cannot afford their coinsurance may be eligible for assistance from the manufacturer and third-party foundations. At completion of therapy, the device and system parts are returned to the manufacturer.

### Other Solid Tumors

TTFields are being studied at therapeutic intensities to treat solid tumors in the thorax (NSCLC, mesothelioma, squamous cell lung cancer), abdomen (pancreatic cancer), central nervous system (brain metastases from NSCLC), and pelvis (ovarian cancer). This novel treatment provides an opportunity for tumor response with potentially fewer side effects than with other treatments.

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## CHAPTER 17

# Tumor-Treating Electric Fields for Glioblastoma

Kenneth D. Swanson, PhD<sup>a</sup>, Edwin Lok, MS<sup>a</sup>, Eric T. Wong, MD<sup>a,b,\*</sup>

### HISTORICAL CONTEXT OF ELECTRIC FIELD TREATMENT

The application of physical energy from various parts of the electromagnetic spectrum is common in glioblastoma treatment. The most widely used involves energies from the higher end of the spectrum in exahertz (the  $10^{18}$ -Hz range), in which ionizing radiation is used to treat various types of malignancies, including glioblastoma (Fig. 17.1). Therapeutic radiation can be diffuse, as in whole-brain and involved-field radiotherapy, or highly conformal, as in stereotactic radiosurgery (SRS), and the biological responses to these different types of radiation are different, as modeled by the linear-quadratic dose-effect relationship.<sup>1-3</sup> At the lower end of the spectrum, in the gigahertz or  $10^9$ -Hz microwave range, laser interstitial thermal therapy (LITT) is being used for the thermocoagulation of brain tumors and the treatment of radiation necrosis.<sup>4-6</sup> MRI technology now allows the real-time visualization of temperature changes during LITT treatment of a target lesion. In addition, at an even lower part of the electromagnetic spectrum, in the kilohertz or  $10^3$ -Hz range, alternating electric field therapy or tumor-treating electric fields (TTFields) are now an established treatment for glioblastoma.<sup>7</sup> This chapter provides a summary of the cell biology and physical science effects of TTFields on tumor cells and tumors in the brain, as well as a historical perspective of the clinical studies conducted in the glioblastoma population.

### BIOLOGICAL BASIS AND PHYSICAL SCIENCE SUPPORTING THE USE OF TUMOR-TREATING ELECTRIC FIELDS

#### Cell Biology Effects of Tumor-treating Fields

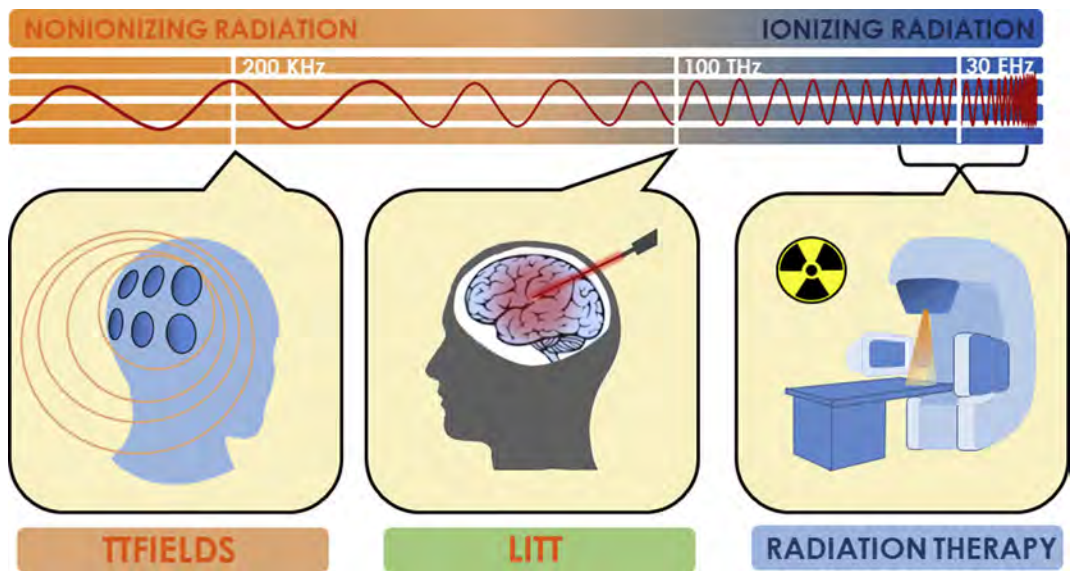
Early *in vitro* studies showed that cells exposed to TTFields underwent violent membrane blebbing during mitosis, thought to be a result of the disruption of alpha/beta tubulin assembly in mitotic spindles.<sup>8,9</sup> More detailed analysis revealed that these cells seem to transit normally through metaphase, showing normal rates of cyclin B destruction and metaphase exit at times consistent with the expected entry into anaphase.<sup>10</sup> However, anaphase and cytokinesis were perturbed, leading to aberrant mitotic exit. Mitosis is dominated by a myriad of processes that must be regulated spatially and temporally in order to ensure even distribution of parental genomic DNA into the resulting daughter cells. Most of the regulatory events during mitosis control functions that are involved in the migration and alignment of chromosomes, as well as the timing of the contraction of the cytokinetic furrow following chromosome separation. Given the timing of the TTField-induced cellular disruption during mitosis, they likely exert their effect on intracellular proteins that are necessary during late metaphase or anaphase and that bear high electric charges on which the TTFields can act. It is not clear whether these TTField effects are caused by their combined activities on multiple proteins or whether they arise from the perturbation of a single protein that serves a critical function. In order to serve as a TTField target,

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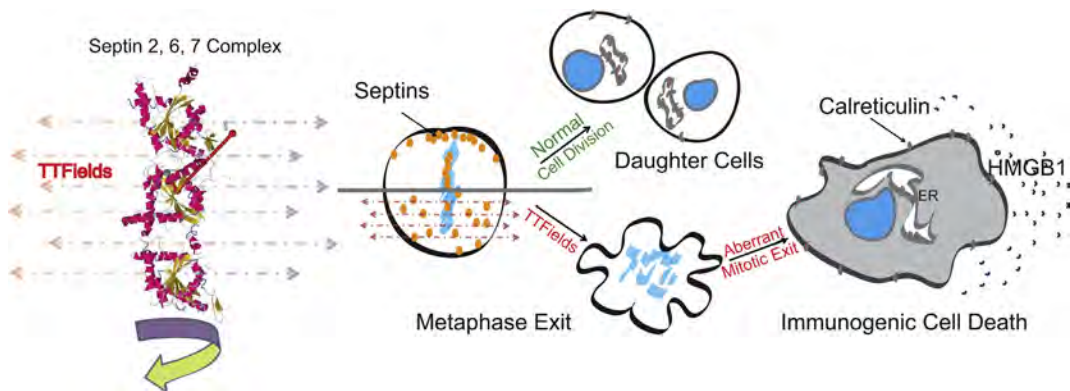


**Fig. 17.1** Application of the electromagnetic spectrum in the treatment of brain tumors. Traditional ionizing radiation has a frequency in the exahertz, or  $10^{18}$  Hz, range, whereas laser-induced thermal therapy uses microwaves in the gigahertz, or  $10^9$  Hz, range to induce thermocoagulation. Tumor-treating electric fields use the lower end of the electromagnetic spectrum in the kilohertz, or  $10^3$  Hz, range. LITT, laser interstitial thermal therapy; TTFIELDS, tumor-treating fields. (Courtesy of Kisa Zhang, BS, Boston, MA.)

proteins must possess a sufficiently high dipole moment in order for the alternating electric fields generated by the TTFIELD therapy device to perturb its function in mitosis.

By examining the published dipole moment database of different proteins, the authors found that the heterotrimeric protein complex composed of septin 2, 6, and 7 possesses a dipole moment of 2711 Debyes (or  $10^{-18}$  statC·cm SI equivalent), which is 5 standard deviations greater than the median value derived from an analysis of more than 14,000 intracellular proteins.<sup>10,11</sup>

Importantly, this septin complex performs important functions during both metaphase and anaphase and its disruption by short hairpin RNA-mediated depletion resulted in blebbing during mitosis similar to that seen in TTFIELD-treated cells.<sup>12</sup> TTFIELDS are able to perturb normal septin localization during mitosis and cell spreading, which strongly suggests that TTFIELDS physically interact with this complex and exert their effects on mitotic cells by preventing the proper localization of this septin-containing complex to proper sites of action during mitosis (**Fig. 17.2**).



**Fig. 17.2** Interaction between TTFIELDS and tumor cells undergoing mitosis. TTFIELDS induce an electromechanical force on the septin 2, 6, and 7 complex that has an extremely large dipole moment of 2711 Debyes. This movement results in mitotic catastrophe and aberrant mitotic exit, leading to an increased cell surface expression of the endoplasmic reticulum chaperonin calreticulin and the secretion of HMGB1, which acts as a danger signal when released from cells, both of which are essential for immunogenic cell death.



The TTFIELD-induced catastrophe during anaphase results in a failure to complete division that results in a G<sub>0</sub>/G<sub>1</sub> arrest and p53-dependent apoptosis. Therefore, TTFIELDS are likely to exert an effect on multiple proteins and the resulting cumulative perturbation may be necessary to drive the observed mitotic catastrophe.

Postmitotic cells that are treated with TTFIELDS and aberrantly exit mitosis develop aneuploidy, and these aneuploid cells are in general resistant to apoptosis, a process that is known to trigger an immunosuppressive response in the host.<sup>13,14</sup> However, TTFIELDS also cause cytoplasmic stress and additional signs of immunogenic cell death, including high mobility group box 1 (HMGB1) secretion into the extracellular space, calreticulin upregulation on the cell surface, and annexin V binding.<sup>15,16</sup> These findings suggest that TTFIELDS may increase the immunogenicity of tumor cells *in vivo*. When highly metastatic VX-2 tumors were injected into the kidney capsules of rabbits and were treated with TTFIELDS for 7 days after their establishment, metastases to the lungs were markedly reduced compared with non-treated animals. Recovered lung metastases also revealed a significant increase in infiltration of immune cells within the tumors.<sup>17,18</sup> An interpretation of these results is that TTFIELDS acted to sensitize the animals against metastatic spread and that the increased leukocytic infiltrates reflected an increased requirement for the immunosuppressive stroma for their establishment and maintenance. As discussed later, patients treated with the immunosuppressive steroidal anti-inflammatory drug dexamethasone seem not to respond to TTFIELD treatments and those with higher levels of CD3<sup>+</sup>, CD4<sup>+</sup>, and CD8<sup>+</sup> lymphocytes are more likely to have a better outcome on this therapy.<sup>19</sup> Collectively, these data strongly support an immunologic basis for the antitumor response from TTFIELD treatment.

### Physical Properties of Tumor-treating Fields and Electric Field Distribution Within the Brain

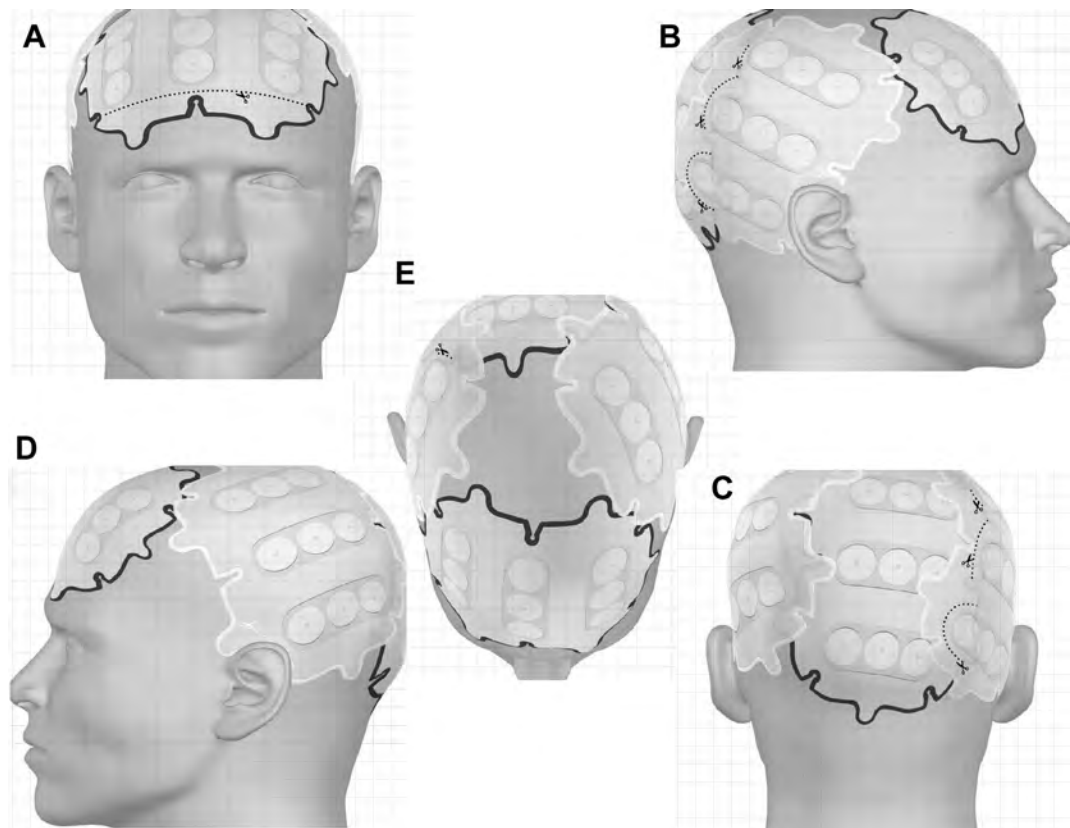
The physical effects of TTFIELDS are governed by the fundamental physics of Gauss' law, Ohm's law, the continuity equation, and Coulomb's law.<sup>20</sup> In addition, several factors, including a medium's electrical conductivity (a measure of the ability to pass charges) and relative permittivity (a measure of the ability to hold charges), can affect the electric field distribution within the brain tissue. Because each tissue type is unique, the intracranial structures must therefore be characterized based on their conductivity and permittivity values. The highly heterogeneous

consistency and geometry of the brain therefore distort the intracranial electric fields as induced by an external source. Electric fields are generally defined by instantaneous changes in electric potential. These changes in electric potential result in electromotive disruption of mitotic structures and are therefore the basis for the therapeutic benefit of TTFIELDS.<sup>9,10</sup> TTFIELD therapy for glioblastoma is delivered by 2 pairs of transducer arrays positioned orthogonally on the shaved scalp, adhered by a thin layer of conductive gel that provides good conductivity (Fig. 17.3).<sup>20,21</sup> TTFIELDS are generated by a battery-powered alternating current generator, operating at 200 kHz with maximum voltage alternating from +50 to -50 V.

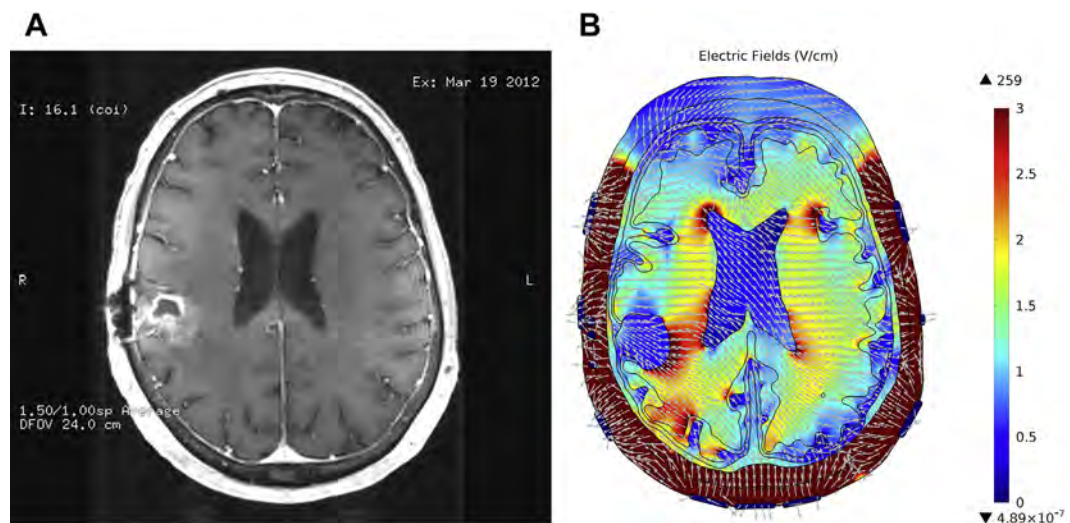
To obtain a comprehensive model of the electric field's distribution in the brain, computer modeling can be performed using coregistered patient DICOM (Digital Imaging and Communications in Medicine) data sets from T1-weighted postgadolinium, T2, and MPRAGE (Magnetization-Prepared Rapid Acquisition with Gradient Echo) MRI. Previously, Lok and colleagues<sup>22</sup> showed a heterogeneous distribution of electric fields in the brain, and the regions adjacent to the ventricular horns had a particularly high electric field intensity (Fig. 17.4). This high field intensity is likely caused by the higher electric conductivity of cerebrospinal fluid than the surrounding tissues, which behaves like the terminal of a capacitor, with the surrounding tissues functioning like a dielectric between conductive terminals. Since a dielectric medium generally retains charge, the rate at which the medium is able to collect and retain the charge is defined by its conductivity and relative permittivity. At 200 kHz, the effect of permittivity is overwhelmed by the conductivity of the medium (Fig. 17.5).<sup>23</sup> Furthermore, each medium has a unique capacitive reactance characteristic of the medium's conductivity, and the rate at which the medium is able to collect and retain charges is frequency dependent. At high frequencies, the medium only has limited time to collect a finite amount of charges and retain them before the field collapses as the polarity changes direction, thereby discharging the initially retained charges before repeating the process.

Because cerebrospinal fluid has a low permittivity value compared with its surrounding tissues, it is a poor dielectric medium and thus charges migrate through the fluid layer at a much faster rate with minimal charge retention. This property explains why most of the cerebrospinal fluid has very low electric field intensity. But this is not true at the interface between cerebrospinal fluid and its adjacent brain tissue. For a perfect solid



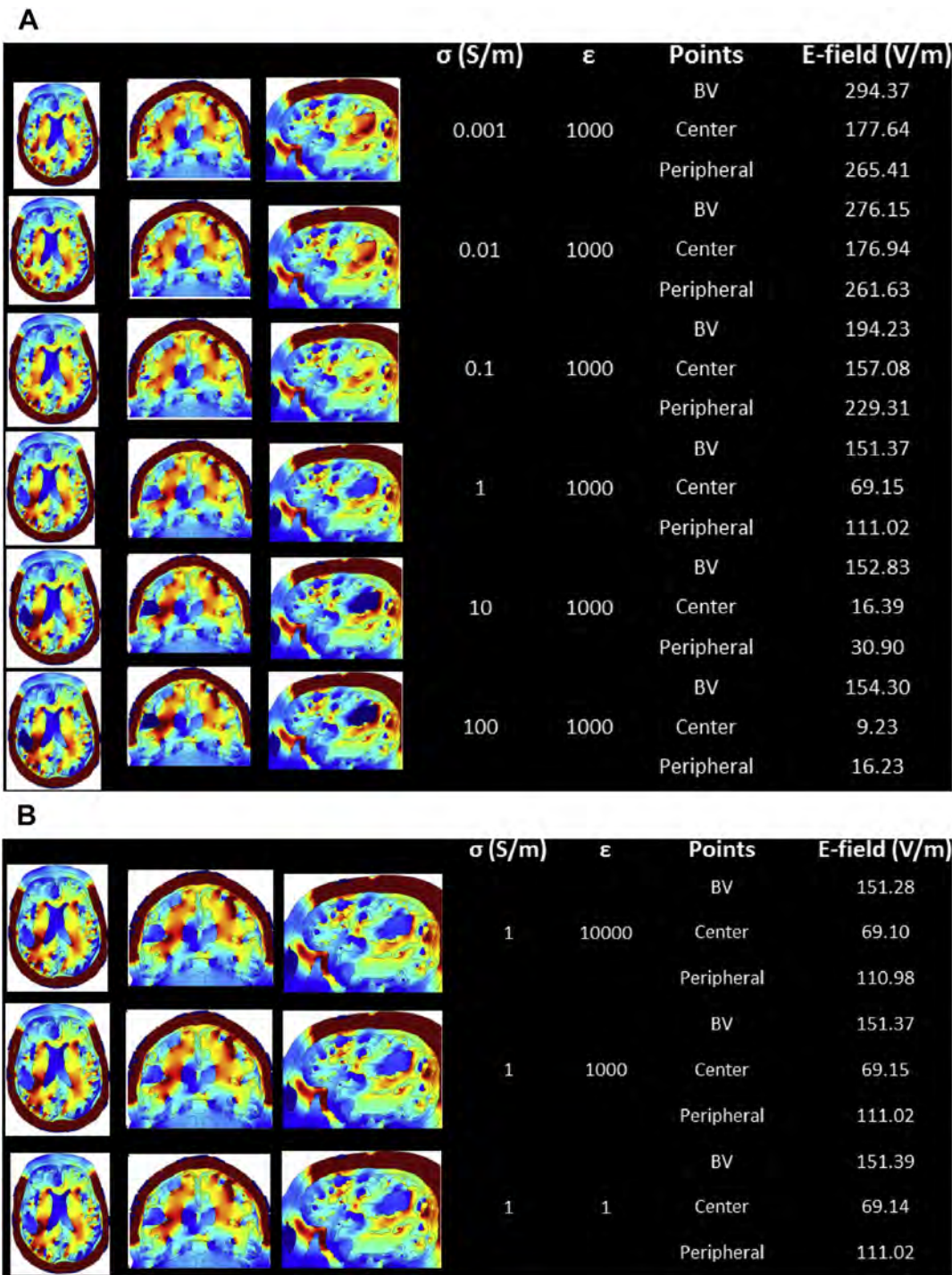


**Fig. 17.3** Transducer array placement for TTFields therapy. TTFields are delivered by 2 pairs of transducer arrays placed orthogonally (A–E) on the shaved scalp. The arrays are connected to a battery-operated current generator, operating at 200 kHz with peak-to-peak voltage from +50 to –50 V.



**Fig. 17.4** Intracranial distribution of TTFields. Computed modeling of a patient’s recurrent glioblastoma in the right parietal brain (A) revealed inhomogeneous electric field distribution within the intracranial space (B). High field strength was seen at the ventricular horns and the medial aspect of the tumor facing the lateral ventricle.





**Fig. 17.5** Sensitivity analysis of the electric field distribution in the gross tumor volume (GTV) as a function of conductivity or permittivity. (A) The electric field intensity of the GTV and the surrounding tissues decreased as the conductivity increased from 0.001 to 100 S/m. (B) However, the electric field intensity and distribution did not change significantly as permittivity varied from 1 to 10,000. BV, bilateral ventricles.

conductor, the electric field within it is zero, and the charges are uniformly distributed on the surface of the conductor. However, cerebrospinal fluid is neither a perfect conductor nor a dielectric.

When charges are positioned across a parallel flat surface, repulsive forces are generated and the charges dissipate away from each other. However, on surfaces with very steep geometric gradients



(ie, sharp corners), the repulsive forces are greatly increased because the charge density is much higher within a smaller surface area. Therefore, it is expected that the ventricular horns have a significantly higher electric field intensity than the rest of the cerebrospinal fluid space as a result of the bunching effect of charge distribution in a region with an irregularly sharp geometry.

The electric properties of gliomas can also vary among patients depending on their tumor composition. Tumors with larger necrotic cores are likely to have higher field intensities in the gross tumor volume because of the capacitive reactance, as explained earlier. In contrast, tumors with smaller or no necrotic core are likely to have lower field intensities at the center of the volume because of absence of an adjacent conductive medium to act as an electric current source. This property may become clinically relevant due to the increased requirement for time of exposure to TTFields as the outer layers of the gross tumor volume are treated by lower field intensities.

## EVIDENCE FOR THE USE OF TUMOR-TREATING ELECTRIC FIELDS IN THE TREATMENT OF RECURRENT AND DE NOVO GLIOBLASTOMAS

### First-in-Human Tumor-Treating Fields Therapy for Glioblastoma

The first-in-human pilot trial for safety and efficacy of TTFields therapy was conducted in Europe from 2004 to 2005 and enrolled 10 patients with recurrent glioblastoma.<sup>8</sup> The most common adverse event was contact dermatitis, which occurred in 9 patients and was thought to be a result of hydrogel-induced irritation on the scalp. Two patients experienced partial seizures that were related to their tumors. No toxicity on blood count or chemistry was seen, except for increased liver enzyme levels in those taking anticonvulsants. The median overall survival (mOS) of the 10 patients was 14.4 months. The time to tumor progression was 6.0 months and the 1-year overall survival (OS) rate was 67.5%, which compared favorably with the historical data of 5.8 months for mOS, 2.1 months for median progression-free survival (mPFS), and 21% for 1-year OS.<sup>8,24</sup> There was 1 complete and 1 partial responder who were alive at 84 and 87 months, respectively, from treatment initiation.<sup>25</sup> Importantly, the intensity of electric fields as directly measured in 1 patient was validated to be within 10% of the values estimated by computer modeling of the electric field distribution within the brain.<sup>8</sup>

A concurrent pilot study was conducted from 2005 to 2007 that enrolled 10 patients with newly

diagnosed glioblastoma.<sup>25</sup> TTFields were added to adjuvant temozolomide after initial standard-of-care radiotherapy and concomitant daily temozolomide.<sup>26</sup> The mPFS was 35.8 months and mOS was greater than 39 months, which compared favorably with the mPFS of 6.9 months and mOS of 14.6 months from the data in the phase III trial.<sup>25,26</sup> The only adverse event noted in the pilot cohort was scalp dermatitis, and that could be ameliorated by topical corticosteroids and periodic shifting of transducer arrays.<sup>25</sup> There were 2 long-term survivors who lived 84 and 64 months from their initial diagnoses.<sup>25</sup>

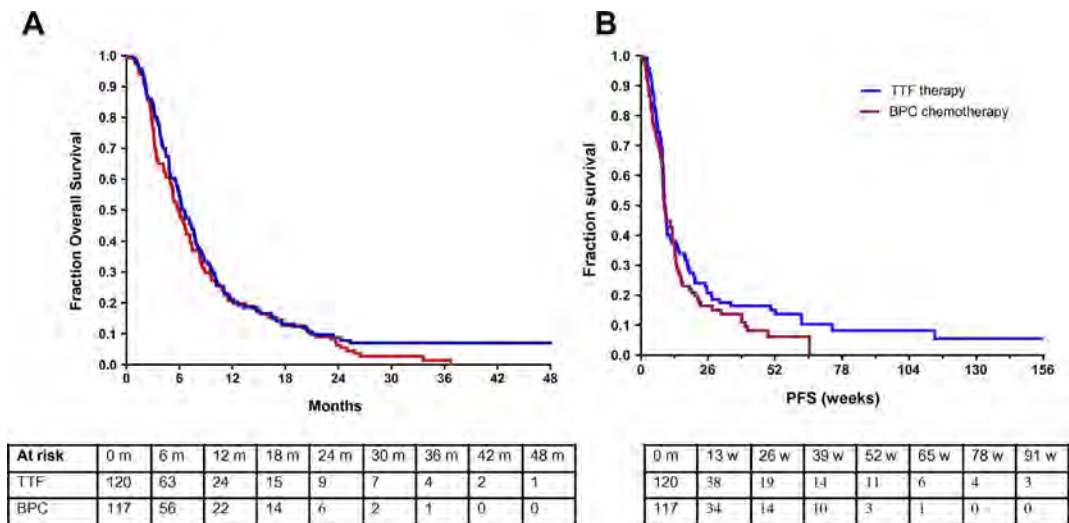
### Tumor-Treating Fields for Recurrent Glioblastoma

The phase III pivotal trial of TTFields for recurrent glioblastoma was conducted from 2006 to 2009 and the primary end point was OS (NCT00379470).<sup>27</sup> In the intent-to-treat population, the median OS was 6.6 months for subjects treated with TTFields versus 6.0 months for those who received best physician's choice (BPC) chemotherapy, with a hazard ratio of 0.86 ( $P = .27$ ) (Fig. 17.6). About 31% of the BPC chemotherapy cohort received bevacizumab alone or in combination with chemotherapy. The mPFS was 2.2 and 2.1 months respectively for TTFields and BPC chemotherapy treatment, with a hazard ratio of 0.81 ( $P = .16$ ). The progression-free survival (PFS) at 6 months was 21.4% and 15.1%, respectively ( $P = .13$ ). The 1-year survival rate was 20% in both cohorts. The outcome of the trial indicated that TTFields probably had efficacy comparable to chemotherapy and bevacizumab.

Grade 1 or 2 scalp irritations were the most common adverse events associated with the device. Shifting the arrays slightly during array exchange and applying topical corticosteroid can minimize this irritation.<sup>28</sup> There were far less hematological toxicity, appetite loss, constipation, diarrhea, fatigue, nausea, vomiting, and pain associated with the device when compared to BPC chemotherapy. Furthermore, analysis showed that device-treated patients had better cognitive and emotional functions. Based on the comparable efficacy results and absence of serious TTField-associated toxicities, the US Food and Drug Administration (FDA) approved TTFields therapy on April 8, 2011 for the treatment of recurrent glioblastoma.

The discrepancy in the OS rates between the results of the phase III trial and the robust outcome from the first-in-human pilot study prompted a series of *post hoc* analyses of the trial data. The first analysis centered on responders. This analysis showed that 5 of 14 responders treated with





**Fig. 17.6** Intent-to-treat Kaplan-Meier OS and PFS curves in the pivotal trial for patients with recurrent glioblastoma comparing TTField therapy with BPC chemotherapy. (A) The median OS was 6.6 months for patients treated with TTFields versus 6.0 months for those received BPC chemotherapy, with a hazard ratio of 0.86 ( $P = .27$ ). (B) The median PFS was 2.2 and 2.1 months respectively for TTFields and BPC chemotherapy treatment, with a hazard ratio of 0.81 ( $P = .16$ ). TTF, TTFields.

TTField monotherapy had prior low-grade histology, whereas none of the 7 responders treated with BPC chemotherapy did.<sup>29</sup> Second, the analysis revealed significantly less dexamethasone use in responders when compared to nonresponders.<sup>29</sup> Responders in the TTField monotherapy group received a median dexamethasone dose of 1.0 mg/d while nonresponders received 5.2 mg/d. A similar difference was also noted in the median cumulative dexamethasone dose of 7.1 mg for responders compared to 261.7 mg for nonresponders. In the chemotherapy cohort, the median dexamethasone dose used was 1.2 mg/d for responders while it was 6.0 mg/d for nonresponders. However, the median cumulative dexamethasone dose was not significantly different: 348.5 mg for responders versus 242.3 mg for nonresponders. These data suggest that TTFields efficacy may be influenced by concurrent dexamethasone use, which is a clinically modifiable factor. This finding prompted an in-depth analysis of the dexamethasone effect in the entire trial population.

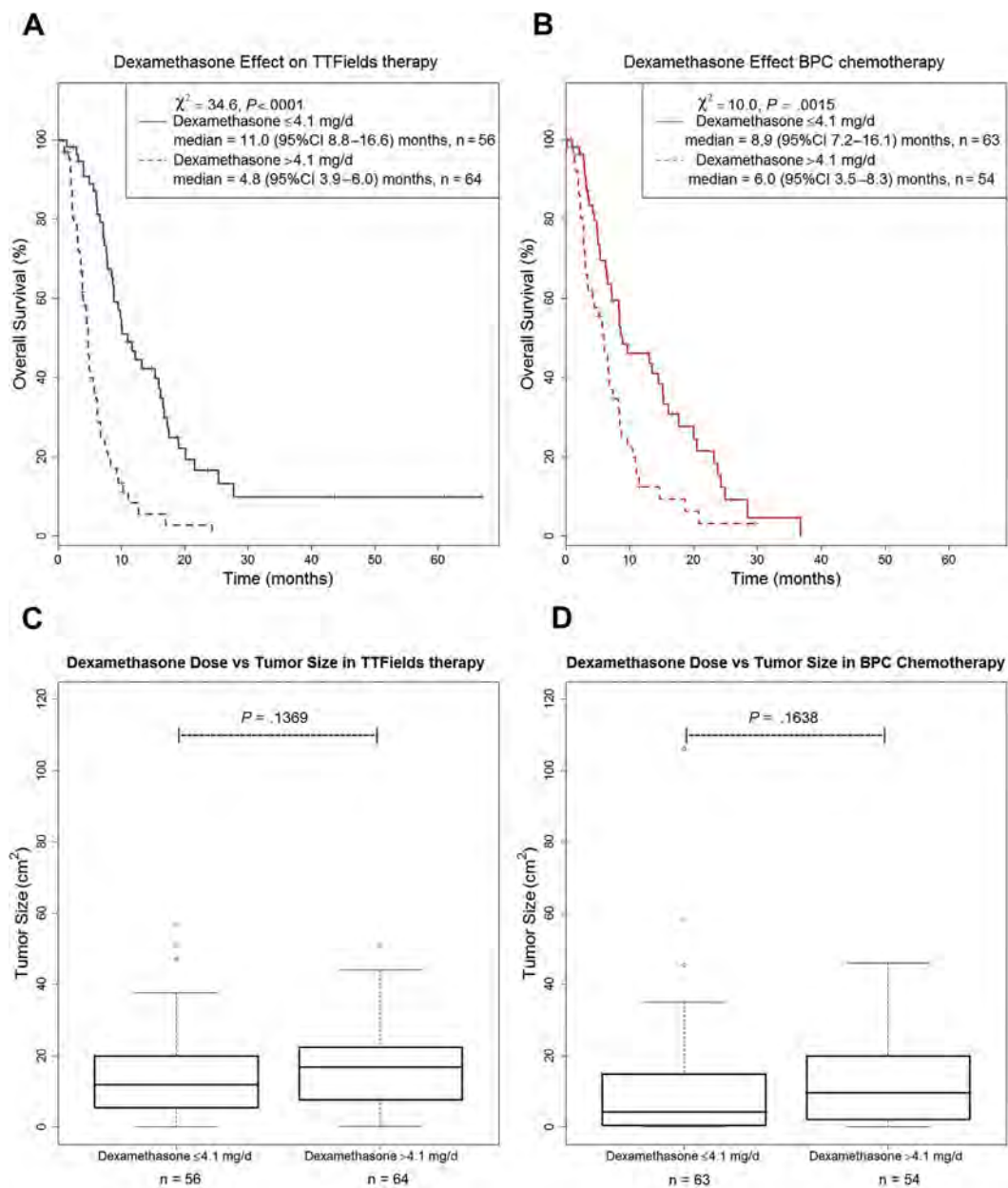
Applying an unsupervised modified binary search algorithm that stratified the TTField monotherapy arm of the phase III trial based on the dexamethasone dosage that provided the greatest statistical difference in survival revealed that subjects who used greater than 4.1 mg/d of dexamethasone had a markedly shortened median OS of 4.8 months compared with those who received less than or equal to 4.1 mg/d, who had a median OS of 11.0 months (Fig. 17.7).<sup>19</sup> Subjects in the chemotherapy arm were observed to have a

similar, but less robust, dichotomization and those who used greater than 4.1 mg/d and less than or equal to 4.1 mg/d of dexamethasone had a median OS of 6.0 and 8.9 months, respectively. This difference in OS based on dexamethasone dose was unrelated to tumor size but was most likely caused by interference with patient immune effector function. A single-institution validation cohort of patients treated with TTField therapy, using their CD3<sup>+</sup>, CD4<sup>+</sup>, and CD8<sup>+</sup> T lymphocyte levels as a marker of immune competency, suggested the importance of immune competence to TTField therapy. Importantly, a dexamethasone dosage of greater than 4.0 mg/d was also a poor prognostic factor in newly diagnosed patients who completed radiotherapy,<sup>30</sup> supporting the conclusion that dexamethasone can interfere with treatment. With successive increases in dexamethasone dosage, both cohorts reached an inflection point near 8.0 mg/d, after which the rate of survival decreased slowly. Taken together, dexamethasone exerts a generalized and profound interference on the efficacy of both TTFields and chemotherapeutic treatment against glioblastoma. Therefore, dexamethasone use should be aggressively minimized.<sup>19,31</sup>

**Use of Tumor-Treating Fields Therapy in Clinical Practice**

The post-FDA-approval usage of TTField therapy in routine clinical practice may differ from that in the registration trial, primarily because clinical trial data may not always be representative of





**Fig. 17.7** Kaplan-Meier OS and tumor size with respect to dexamethasone requirement of less than or equal to 4.1 mg/d versus greater than 4.1 mg/d from subjects enrolled in the phase III trial comparing TTField therapy with BPC chemotherapy. (A) Subjects enrolled in the TTField treatment arm taking dexamethasone less than or equal to 4.1 mg/d (solid blue) versus greater than 4.1 mg/d (dashed blue), which was determined by an unsupervised binary partitioning algorithm. Subjects who used less than or equal to 4.1 mg/d of dexamethasone (n = 56) had a median OS of 11.0 months (95% confidence interval [CI], 8.8–16.6) compared with those who used greater than 4.1 mg/d (n = 64), who had a median OS of 4.8 months (95% CI, 3.9–6.0) ( $\chi^2 = 34.6$ ;  $P < .0001$ ). (B) Subjects enrolled in the BPC chemotherapy arm taking dexamethasone less than or equal to 4.1 mg/d (solid red) versus greater than 4.1 mg/d (dashed red), which was determined by the same unsupervised binary partitioning algorithm. Subjects who used less than or equal to 4.1 mg/d of dexamethasone (n = 63) had a median OS of 8.9 months (95% CI, 7.2–16.1) compared with those who used greater than 4.1 mg/d (n = 54), who had a median OS of 6.0 months (95% CI, 3.5–8.3;  $\chi^2 = 10.0$ ;  $P = .0015$ ). (C) Box-and-whisker plot of bidimensional tumor size in the TTField therapy cohort that received dexamethasone less than or equal to 4.1 mg/d versus greater than 4.1 mg/d. Subjects who took dexamethasone less than or equal to 4.1 mg/d (n = 56) had a median tumor size of 11.9 cm<sup>2</sup> (range, 0.0–56.7 cm<sup>2</sup>) compared with those who used greater than 4.1 mg/d (n = 64), who had a



treatment outcome in routine clinical practice environments. Reasons for this discrepancy may arise from the prespecified clinical characteristics that trial subjects must possess that real-world patients may not have. As a result, trial subjects typically have healthier neurologic functions, better performance status, and fewer medical comorbidities, all of which may enable trial subjects to benefit more from the new treatment. Furthermore, the FDA must strike a fine balance between providing the public rapid access to new treatments for deadly diseases and requiring comprehensive data and protracted reviews on their benefits and risks. This action sometimes results in the reversal of prior accelerated approval decisions. Therefore, these issues prompted the development of the Patient Registry Data Set (PRiDe) to capture data on TTField usage among patients in the routine clinical practice environment.

PRiDe consisted of 457 patients from 91 treatment centers in the United States. Patients treated in PRiDe had a median OS of 9.6 months compared with 6.6 months in the TTField monotherapy arm in the registration trial.<sup>27,32</sup> The 1-year OS rate was also longer at 44% compared with 20%, respectively.<sup>27,32</sup> The difference in survival characteristics is most likely caused by the higher proportion of patients treated with TTFields at first recurrence in PRiDe (33%) than in the registration trial (9%). Treatment at an earlier timepoint in the disease process may provide a higher efficacy than treatment at a later timepoint. Absence of prior bevacizumab usage was also favorable.<sup>32</sup> Nevertheless, the heterogeneity in the adjunctive treatments used in conjunction with TTField therapy in PRiDe that was not adequately captured, which included cytotoxic chemotherapy, bevacizumab, or even alternative medicine, is an important caveat that makes it statistically noncomparative with the TTField monotherapy arm in the phase III trial.

### Efficacy of Tumor-Treating Fields Therapy for Newly Diagnosed Glioblastoma

A phase III randomized open-label study of TTField therapy was conducted in 700 patients with newly diagnosed glioblastoma between 2009 and 2014 (NCT00916409). After their initial

radiotherapy and concomitant daily temozolomide, subjects were randomized in a 2:1 fashion to receive either TTFields plus maintenance temozolomide or maintenance temozolomide alone.<sup>33</sup> The primary end point was PFS. In a prespecified interim analysis of the first 315 subjects after a minimum follow-up of 18 months, the intent-to-treat cohort that received TTFields plus temozolomide had a longer PFS than the cohort treated with temozolomide alone: median 7.1 versus 4.0 months (hazard ratio = 0.62; 95% confidence interval [CI], 0.43–0.89; log rank  $P = .0014$ ) (Fig. 17.8). The median OS also favors the TTFields plus temozolomide group, at 19.6 versus 16.6 months respectively (hazard ratio = 0.74; 95% CI, 0.56–0.98; log rank  $P = .034$ ), as well as the per protocol population that completed more than 1 cycle of treatment, at 20.5 versus 15.6 months respectively (hazard ratio = 0.64; 95% CI, 0.42–0.98; log rank  $P = .004$ ).

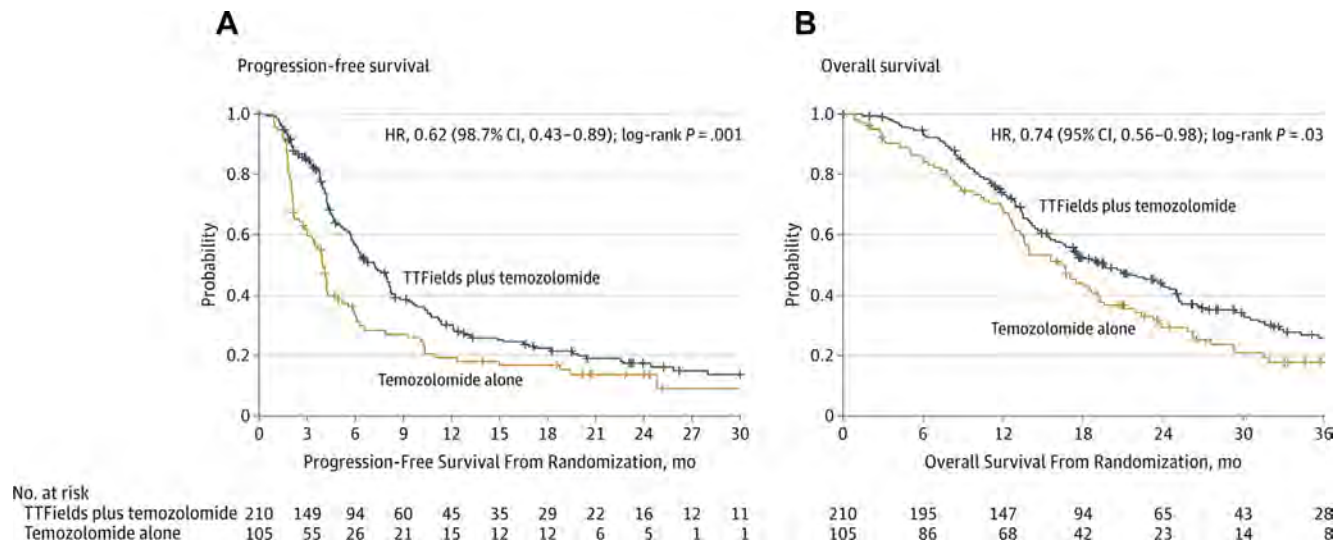
The trial population experienced no unexpected adverse events.<sup>33</sup> Grade 3 and 4 hematological toxicities between the TTFields plus temozolomide and temozolomide alone cohorts (12% vs 9%), gastrointestinal disorders (5% vs 2%), and convulsions (7% vs 7%) were not significantly different. Only scalp reaction was more commonly seen in those who received TTFields plus temozolomide. Based on the favorable efficacy and toxicity data, the US FDA granted approval on October 5, 2015 to use TTFields in conjunction with maintenance temozolomide in the adjuvant setting for patients with newly diagnosed glioblastoma.

### SUMMARY

Human clinical trial testing of TTField efficacy was started in neuro-oncology, initially for the treatment of recurrent glioblastoma (NCT00379470) and later in newly diagnosed glioblastoma (NCT00916409).<sup>27,33</sup> This route of development for a new anticancer therapy is highly unusual because treatments in neuro-oncology were traditionally adopted from established therapies from other disease sites, when the accompanying preclinical scientific data on the mechanisms of action had been firmly established. Nevertheless, the 2 pivotal trials conducted in glioblastoma have

median tumor size of 16.8 cm<sup>2</sup> (range, 0.3–51.0 cm<sup>2</sup>). ( $P = .1369$ ). (D) Box-and-whisker plot of bidimensional tumor size in the BPC chemotherapy cohort that received dexamethasone less than or equal to 4.1 mg/d versus greater than 4.1 mg/d. Subjects who took dexamethasone less than or equal to 4.1 mg/d ( $n = 63$ ) had a median tumor size of 4.2 cm<sup>2</sup> (range, 0.0–11.2 cm<sup>2</sup>) compared with those who used greater than 4.1 mg/d ( $n = 54$ ), who had a median tumor size of 9.6 cm<sup>2</sup> (range, 0.0–46.0 cm<sup>2</sup>) ( $P = .1638$ ).





**Fig. 17.8** Prespecified interim analysis of PFS and OS in registration trial for patients with newly diagnosed glioblastoma comparing maintenance TTField therapy plus temozolomide versus temozolomide alone. Kaplan-Meier comparison of the two cohorts showed (A) a median PFS of 7.1 versus 4.0 months respectively, with a hazard ratio of 0.62 ( $P = .0014$ ), and (B) a median OS of 19.6 versus 16.6 months respectively, with a hazard ratio of 0.74 ( $P = .034$ ).



helped to established TTFields as a *bona fide* anti-cancer treatment and its efficacy is being actively investigated in glioblastoma as well as other malignancies both within and outside the central nervous system.

To improve the efficacy of TTFields treatment of recurrent glioblastomas, there is a strong rationale for combining it with SRS. Large-fraction radiotherapy might potentiate immune-mediated antitumor activity.<sup>34,35</sup> The addition of TTFields after SRS may further potentiate this effect because exposed tumor cells show cell surface expression of calreticulin and secretion of HMGB1, both of which are required to generate immunogenic cell death.<sup>15,36,37</sup> Furthermore, a *post hoc* analysis of the phase III trial for recurrent glioblastoma showed that the application of TTFields among subjects who had progressed on bevacizumab ( $n = 23$ ) resulted in a longer mOS of 6.0 months compared with a mOS of 3.3 months ( $n = 21$ ) in those treated with BPC chemotherapy (hazard ratio = 0.43; 95% CI, 0.22–0.85;  $\chi^2 P = .06$ ).<sup>38</sup> In addition, the favorable intracranial safety profile of TTFields and bevacizumab suggests that the combination will most likely have an acceptable level of toxicity.<sup>38,39</sup> There is a planned Radiation Therapy Oncology Group foundation study on TTFields and bevacizumab in patients with recurrent glioblastoma who have progressed while on bevacizumab.

Several investigator-initiated combination trials are being conducted using (1) TTFields in combination with bevacizumab and carmustine in patients with glioblastoma at first relapse (NCT02348255), (2) TTFields with bevacizumab and hypofractionated stereotactic radiotherapy for bevacizumab-naïve patients with recurrent glioblastoma (NCT01925573), and (3) TTFields in combination with temozolomide and bevacizumab for patients with newly diagnosed glioblastoma in the maintenance phase of treatment, after initial radiotherapy with concomitant temozolomide and bevacizumab (NCT02343549). In addition, a study has been designed to find genomic signatures of recurrent glioblastoma that may correlate with response to TTFields (NCT0194576). Collectively, these planned and ongoing studies indicate the current state of interest in combining TTFields with other established modalities of treatment for glioblastoma.

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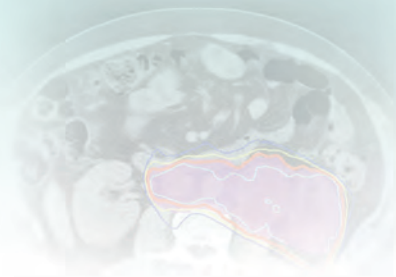
## ACKNOWLEDGMENTS

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# High-Grade Gliomas

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and Benjamin W. Corn



## INCIDENCE

There are approximately 68,000 new cases of brain tumors diagnosed in the United States each year. Gliomas now account for nearly 80% of malignant brain tumors. Glioblastoma (GBM) is the most common primary malignant brain tumor.<sup>1</sup>

## BIOLOGIC CHARACTERISTICS

A better prognosis is associated with grade III tumors (as classified by the World Health Organization [WHO]) when compared with grade IV tumors (i.e., GBM) and for oligodendrogliomas when compared with astrocytomas. A better response to therapy and higher rates of survival are associated with oligodendroglial tumors manifesting 1p19q codeletions and IDH mutations. Methylation of the promoter for the *MGMT* gene predicts for increased sensitivity to DNA alkylating agents such as temozolomide and is prognostic for overall survival (OS) in patients with GBM, especially older patients.

## STAGING EVALUATION

Optimal imaging is carried out with contrast-enhanced magnetic resonance imaging (MRI). Computed tomography (CT) scans are primarily used as an infrastructure for radiation treatment planning before fusion with MRI images. On the first postoperative day, an MRI study should be obtained to evaluate the extent of resection and as a basis for radiation treatment planning.

## PRIMARY THERAPY AND RESULTS

The standard of care for the definitive treatment of newly diagnosed GBM in patients aged 18 years to 70 years is the delivery of approximately 60 Gy of fractionated partial brain radiotherapy following maximal safe surgical debulking. Irradiation (most commonly administered with conformal strategies) should be accompanied by concurrent temozolomide chemotherapy. Adjuvant temozolomide is also administered for at least 6 months following the end of radiotherapy unless disease progression occurs.

Temozolomide has not been established as a component of standard therapy for newly diagnosed WHO grade III gliomas; ongoing trials are investigating this issue.

Prospective randomized trials could not define a role for either brachytherapy or radiosurgery in the initial management of high-grade gliomas.

## LOCALLY ADVANCED DISEASE AND RECURRENCE

Bevacizumab has been approved for salvage of failures following definitive therapy for GBM. If chemotherapeutic options are not available in the setting of recurrence, creative radiotherapeutic strategies (e.g., radiosurgery, intensity-modulated radiation therapy [IMRT], brachytherapy) may be considered.

High-grade gliomas are almost universally fatal. Although recently discovered combined-modality approaches have prolonged survival, many patients succumb relatively quickly, and cure remains elusive for the majority.

New protocols have recently emerged after decades of limited progress in the management of these tumors. New chemotherapeutic drugs, such as temozolomide, have found application in GBM. Bevacizumab is effective in recurrent disease and prolongs radiographic disease control in first-line regimens. In the future, molecular profiling may also allow tailoring of specific treatment to the patients most likely to benefit.

## ETIOLOGY AND EPIDEMIOLOGY

Most malignant brain tumors are high-grade gliomas, and most of these are GBM, a WHO grade IV tumor. The remainder are WHO grade III tumors such as anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma. Men are more commonly affected than women. The peak incidence occurs in the age range of 65 years to 75 years, and the median survival time is inversely proportional to age; these findings have prompted a redoubling of efforts in elderly subpopulations.<sup>1</sup>

There has been concern for cancer development following exposure to electromagnetic fields, but definitive evidence is lacking. More recently, the use of cellular telephones has been studied extensively in Europe,<sup>2</sup> but its importance as a risk factor has not been established. In terms of chemical exposure, nitrosamines have long been regarded as culpable, but causality is far from proven.<sup>3</sup> Brain tumors have also been linked with previous exposure to therapeutic ionizing radiation.<sup>3</sup> However, the absolute risk is low.

Most gliomas are sporadic, but genetic susceptibility is suspected based on the occurrence of multiple brain tumors in families with germline mutation of the *TP53* suppressor gene and patients with neurofibromatosis type I as well as the rare patients who have been diagnosed with Turcot's syndrome. A heritable syndrome contributes to less than 5% of GBMs.<sup>4</sup>

## PREVENTION AND EARLY DETECTION

No viable strategy for screening or early detection of glial tumors has been developed. There is also no convincing evidence demonstrating either improved survival when high-grade gliomas are found early, or a clear rationale for prophylactic strategies to reduce the incidence of these aggressive tumors.<sup>3</sup>



## BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Investigators around the world are searching for the molecular biologic characteristics of gliomas in an effort to improve therapy. For example, work by the Cancer Genome Atlas Research Network<sup>5</sup> and others<sup>6,7</sup> suggests that at least three molecular subclasses of GBM exist with potential therapeutic and prognostic implications. Mouse modeling has also demonstrated the oncogenic importance of abnormalities in receptor signaling (e.g., epidermal growth factor receptor [EGFR] and platelet-derived growth factor receptor [PDGFR]), signal transduction cascades (e.g., RAS and AKT), and cell cycle regulation.<sup>8</sup>

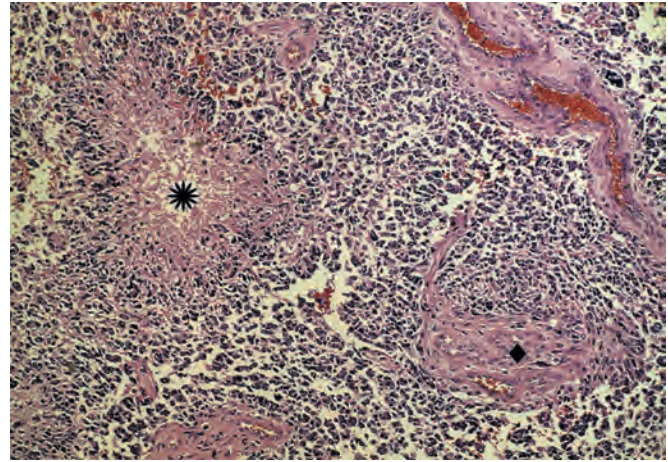
In the early 1990s, it was recognized that deletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) occurs in most oligodendrogliomas.<sup>9</sup> Codeletion of 1p and 19q is prognostic for longer survival,<sup>10-12</sup> although until recently controversy existed as to whether this finding should alter therapy.<sup>13</sup> It is now recognized that an unbalanced chromosomal translocation underlies 1p/19q codeletion,<sup>14,15</sup> but the specific genes involved and their mechanism of action remain elusive. More recently, mutations in the isocitrate dehydrogenase 1 and 2 (*IDH1* and *IDH2*) genes, occurring most often in low-grade gliomas but also in a minority of WHO grades III and IV tumors have been described,<sup>16,17</sup> and are prognostic for longer survival.<sup>12,16,18,19</sup> Methylation of the *MGMT* promoter (see the section on [chemotherapy](#)) is emerging as a potential but imperfect predictive and prognostic factor in the treatment of newly diagnosed GBMs.

With the exception of 1p19q codeletion in anaplastic tumors, it is not yet clear how to best incorporate molecular data into the treatment of individual patients. Detailed discussions of the biologic characteristics of glioma and their clinical relevance are beyond the scope of this chapter and can be found elsewhere.<sup>20</sup>

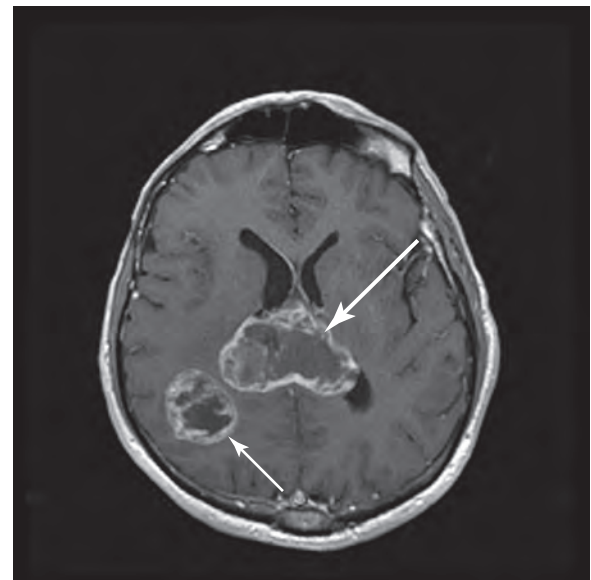
## PATHOLOGY AND PATHWAYS OF SPREAD

The WHO classification system<sup>21</sup> is derived in part from the correlation between pathologic findings and survival rates observed by Bailey and Cushing<sup>22</sup> and published in the early 1900s. In current parlance, *low grade* refers to WHO grades I to II tumors and *high grade* to WHO grades III to IV tumors (Figure 27-1). However, the WHO grade I gliomas (e.g., juvenile pilocytic astrocytomas) are biologically different tumors from the others, infrequently occur in adults, and may be amenable to surgical cure. *Anaplastic* in the context of gliomas refers to WHO grade III tumors such as anaplastic astrocytomas, anaplastic oligodendrogliomas, and anaplastic oligoastrocytomas. GBM is a WHO grade IV astrocytoma, although the most recent WHO classification scheme does account for other rare subtypes, including GBM with oligodendroglial components.

WHO grades II to IV gliomas are characterized by a tendency to directly infiltrate adjacent brain tissue. Lesions with direct access to the corpus callosum may extend across the midline and configure themselves in a classic “butterfly pattern” (Figure 27-2). MRI underestimates the extent of invasive disease, and the diffusely infiltrative nature of these tumors makes complete removal of all tumor cells impossible. This “misleading appearance of enucleability” was described more than 80 years ago.<sup>22</sup> Leptomeningeal spread occurs occasionally (Figure 27-3). Hematogenous and lymphatic spread are exceedingly uncommon.<sup>23</sup>



**Figure 27-1** Highly cellular astrocytic glioma with foci of microvascular proliferation (asterisk) and pseudopalisading necrosis (diamond) consistent with glioblastoma.



**Figure 27-2** “Butterfly” glioblastoma (long arrow); a separate satellite lesion in the right parietal lobe (short arrow) is also apparent. The contrast enhancement with central necrosis is classic for a glioblastoma, which was histologically confirmed by biopsy.

## CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

No specific symptom constellation is pathognomonic of high-grade glioma. Typically, patients present with some combination of headaches, neurologic deficits, nausea, and vomiting, depending on tumor size and location. It is not unusual for patients to present with or subsequently develop seizures. Tissue for pathologic diagnosis can be obtained via stereotactic biopsy, open biopsy, or gross resection in the context of craniotomy. More complete resection improves diagnostic accuracy, provides additional tissue for molecular analyses, and is increasingly thought to improve OS.

The typical imaging appearance of a GBM is a ring-enhancing or heterogeneously enhancing lesion. The differential diagnosis may include stroke, brain metastasis, primary central nervous system lymphoma, demyelination, and even infectious or other inflammatory diseases. If a brain metastasis



is suspected, it is prudent to perform an appropriate extracranial evaluation to identify the primary malignant tumor. If there is a high index of suspicion for primary central nervous system lymphoma, such as in multifocal, periventricular, or homogeneously enhancing lesions,<sup>24</sup> corticosteroids should be withheld preoperatively unless herniation is imminent because their use may confound the histologic diagnosis.

Nearly all GBMs demonstrate contrast enhancement. However, up to 10% of anaplastic gliomas will not manifest such a pattern on imaging. Background uptake in the brain (an organ with an inherent avidity for glucose) significantly compromises the use of glucose-based positron emission tomography (PET) as a diagnostic tool for high-grade gliomas.

An algorithm for the evaluation and management of patients with GBM is shown in Figure 27-4.



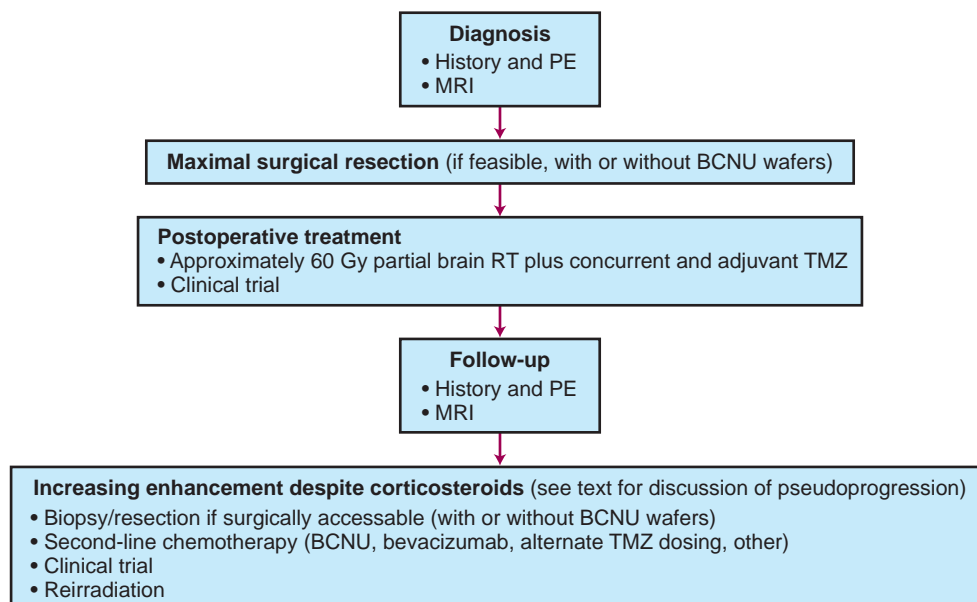
**Figure 27-3** T1 contrast-enhanced sagittal view from a magnetic resonance imaging showing rare leptomeningeal spread from a glioblastoma surrounding the spinal cord.

## PRIMARY THERAPY

### Prognostic and Predictive Factors

Historically, all high-grade gliomas were lumped together in most clinical trials, thereby confounding results because of maldistribution of patients with differing prognoses. In 1993, Curran et al<sup>25</sup> published a landmark paper describing a prognostic classification scheme based on clinical variables. Data from three Radiation Therapy Oncology Group (RTOG) trials that enrolled nearly 1600 patients with high-grade glioma from 1974 to 1989 were used. This recursive partitioning analysis (RPA) methodology builds decision trees to model predictors by examining all possible “cut points” for all variables included in the model. Patients were segmented into six distinct groups with different survival outcomes. The key variables included patient age, performance status, histologic tumor type (i.e., anaplastic astrocytoma versus GBM), mental status, symptom duration antecedent to diagnosis, extent of resection, neurologic function, and radiotherapy dose. Median survival ranged from 4.6 months for class VI patients to almost 5 years for class I patients, underscoring heterogeneity. The European Organization for Research and Treatment of Cancer (EORTC) demonstrated that the prior RTOG RPA classification remained valid among patients in a more recent Phase III trial.<sup>26</sup> An RPA for anaplastic oligodendroglial tumors has also been proposed.<sup>27</sup>

One of the more controversial factors in the setting of high-grade gliomas has been the extent of surgical resection. Bailey and Cushing observed longer survival following resection in their 1926 publication,<sup>22</sup> as did others in the 1960s.<sup>28</sup> Numerous series since then also support more complete resection as a prognostic factor.<sup>29-33</sup> One of the largest involved more than 400 patients at the M. D. Anderson Cancer Center and demonstrated improved median survival (13 versus 8.8 months;  $p < 0.0001$ ) following at least 98% resection, as defined by postoperative MRI scans.<sup>34</sup> One small randomized study of 30 patients older than 65 years demonstrated improved survival rates following resection versus biopsy alone.<sup>32</sup> Use of 5-aminolevulinic acid fluorescence intraoperatively improves the likelihood of gross total resection,<sup>29</sup> but the effect on survival is debated.



**Figure 27-4** Algorithm for diagnosis and treatment of glioblastoma. See text for details. BCNU, Carmustine; MRI, magnetic resonance imaging; PE, physical examination; RT, radiotherapy; TMZ, temozolomide.



## Surgery

Patients can often undergo a craniotomy where the goal is the safe removal of the largest possible volume of tumor to establish a diagnosis and relieve mass effect. High-grade gliomas are not surgically curable because of their extensive infiltration.

If biopsy rather than resection is pursued, choices include stereotactic options with CT or MRI guidance or open craniotomy and biopsy. Some have employed metabolic imaging such as magnetic resonance spectroscopy (MRS) to better select the biopsy sites most likely to contain the most aggressive portions of the tumor, but this is not widely used. Usually, stereotactic biopsy can be performed using either frame-based or frameless neuronavigation systems. The pathologist can review the frozen section to make an immediate preliminary diagnosis and confirm tissue adequacy.

When craniotomy is contemplated, meticulous planning is invested in the scalp incision and flap design. Special care must be taken to preserve the vascular supply of the scalp. The bony opening is devised to be sufficiently large to facilitate resection without needlessly exposing adjacent brain to the risk of injury. After opening the scalp, burr holes are placed and connected with a craniotomy. The bone flap is removed and the dura mater is opened. As a rule, the bone flap is reattached at the end of the resection, although some surgeons prefer not to reattach the bone flap.

Although tumors on the brain surface are immediately visible after exposure, subcortical lesions are harder to discern. Frameless image-guided neuronavigation systems are employed to localize subcortical tumors along with intraoperative ultrasound and MRI. Tumors that are situated near “eloquent” areas of cortex, such as those harboring motor and speech function, are mapped intraoperatively via electrical cortical stimulation to achieve maximal tumor debulking without operative morbidity. Resection of gliomas in the dominant hemisphere is often carried out under local anesthesia with supplementary sedation to allow speech mapping.

Occasionally, tumors may be removed en bloc via circumferential dissection, but more frequently, resection is effected in piecemeal fashion. A cavitation ultrasonic surgical aspirator (CUSA) facilitates removal of a firm, adherent, or calcified tumor.

Patients are routinely monitored in an intensive care unit following a craniotomy. The first MRI is obtained within 24 hours to 48 hours after surgery before postoperative changes set in. The extent of resection can be determined in this manner.

## External Beam Irradiation

External beam irradiation (EBRT) has historically been the cornerstone of the therapeutic approach to GBM (and anaplastic astrocytoma) for the past half-century, and its use in brain tumors was already described by the 1920s.<sup>35</sup> In the 1970s and early 1980s, categorical level I data became available from several studies,<sup>36</sup> including prospective Phase III trials conducted by the Brain Tumor Study Group (BTSG)<sup>37,38</sup> (Table 27-1).

The radiotherapeutic approach to high-grade glioma has evolved. Initially, large opposed lateral fields were employed to cover the entire brain volume. In 1989, Shapiro et al<sup>42</sup> published data from Brain Tumor Cooperative Group trial 80-01, in which the randomization was altered during the trial to compare partial brain irradiation with whole-brain radiotherapy (WBRT). No difference in OS or change in the patterns of failure was seen. Accordingly, WBRT is generally not advocated, except perhaps in the scenario of a widespread intracranial process such as gliomatosis cerebri.<sup>43</sup>

Several lines of evidence have influenced the trend to treat the gross tumor volume along with a margin of approximately 2 cm. In a classic paper published in 1980, Hochberg and Pruitt<sup>44</sup> used CT scans to determine that nearly 90% of GBM recurrences occurred within 2 cm of the primary tumor site (although this may be changing with the use of bevacizumab). Wallner et al<sup>45</sup> assessed the patterns of recurrence in 32 patients with unifocal malignant gliomas who were treated with primary surgery and postoperative irradiation. Nearly 80% of patients manifested recurrence or progression within 2 cm of the original tumor. Even when 80 Gy of partial brain irradiation was used in a prospective Phase I trial,<sup>46</sup> 90% of patients failed within the high-dose region.

It has been demonstrated on biopsy and autopsy studies that the abnormality detected on T2 or fluid-attenuated inversion-recovery (FLAIR) images harbors microscopic tumor extension. Accordingly, 45 Gy to 50 Gy is generally delivered, in 1.8-Gy to 2-Gy fractions, to the T2/FLAIR abnormality seen

**TABLE 27-1** Positive Phase III Trials Evaluating the Role of Irradiation, Chemotherapy, or Chemoradiation in the Treatment of Malignant Gliomas

Study	No. Patients	Treatment Arm	Median (mo)	18 mo	24 mo	5 yr
BTSG 69-01 <sup>37</sup>	VSG		—			
	31	Observation	3.2	0	0	0
	51	Carmustine	4.3	4	0	0
	68	Radiation therapy	8.3	4	1	NA
	72	Radiation therapy plus carmustine	7.9	19	5	NA
BTSG 72-01 <sup>38</sup>	VSG		—			
	81	Semustine	4.8	10	8	NA
	94	Radiation therapy	8.3	15	10	NA
	92	Radiation therapy plus carmustine	11.8	27	15	NA
	91	Radiation therapy plus semustine	9.7	23	12	NA
EORTC/NCI-C <sup>139-41</sup>	286	Radiation therapy	12.1	21	11	2
	287	Radiation therapy plus temozolomide	14.6	39	27	10

BTSG, Brain Tumor Study Group; EORTC, European Organization for Research and Treatment of Cancer; NA, not available; NCI-C, NCI Canada; VSG, valid study group; yr, year.

\*p = 0.001 for radiation therapy versus observation/supportive care and radiation therapy plus carmustine versus observation/supportive care.

†p ≤ 0.003 for radiation therapy, radiation therapy plus carmustine, and radiation therapy plus semustine versus semustine alone.

‡p < 0.0001. Most patients randomized to radiation therapy alone crossed over to temozolomide at time of relapse or progression.



on the image, followed by a boost to raise the total dose to 60 Gy based on the T1-enhancing abnormality. The MRI abnormalities, however, remain quite nonspecific in terms of histopathologic confirmation, and even when novel strategies such as MRS are used for radiotherapy planning, there can be over or underestimation of the true extent of microscopic spread.<sup>47</sup>

A novel view of target definition has recently been proposed.<sup>48,49</sup> This approach posits that neuroprogenitor cells in the subventricular zone (SVZ) play a role in tumor recurrence. In retrospective analyses of dose distribution among patients with GBM, investigators found that the deposition of high dose (e.g., >40 Gy) in the ipsilateral SVZ was associated with a significantly improved progression-free survival (PFS) and OS in patients who also achieved gross total resection of their tumors. To validate this hypothesis, prospective clinical trials will need to be conducted to determine if cancer stem cells will need to be encompassed when delineating the targets for irradiation of high-grade glioma.

### Rationale for Current Total Irradiation Dose

A pooled analysis of three successive randomized trials conducted by the Brain Tumor Study Group (BTSG 66-01, 69-01, 72-01, respectively) generated data to support doses in excess of 50 Gy.<sup>50</sup> A stepwise improvement in survival was observed with doses ranging from less than 45 Gy to 60 Gy, consistent with dose response. A comparison of 70 Gy versus 60 Gy demonstrated no survival or local control advantage for the 70-Gy dose.<sup>51,52</sup> These results established 60 Gy as the standard of care.

Dose escalation has remained an important investigational option because there is still a pattern of failure characterized by local progression or recurrence. There are now multiple techniques for dose escalation, including three-dimensional conformal irradiation, radiosurgery, and brachytherapy, but these have not yielded higher rates of disease control or survival. Increasing the radiotherapy dose or reirradiation with radioprotective or antiangiogenic agents may be a useful strategy in the future.<sup>53</sup>

### Altered Fractionation

The RTOG has systematically and rigorously studied hyperfractionation for high-grade gliomas. In RTOG 83-02, patients were randomized to one of four dose arms (64.8 Gy, 72 Gy, 76.8 Gy, or 81.6 Gy) using twice-daily fractions of 1.2 Gy. Initial results suggested the superiority of 72 Gy,<sup>54</sup> but a subsequent Phase III trial demonstrated no improvement.<sup>55</sup> Prados et al<sup>56</sup> used an elegant randomization to assess not only a hyperfractionation schedule, but also to determine the activity of difluoromethylornithine (DFMO), a compound that inhibits sublethal and potentially lethal damage repair. Unfortunately, neither intervention improved survival.

### Stereotactic Irradiation

Two provocative small-scale experiences prompted the design of Phase III trials to formally evaluate radiosurgery for high-grade gliomas.<sup>57,58</sup> Loeffler et al<sup>57</sup> reported on 37 patients treated with 59.4-Gy fractionated radiotherapy followed by a stereotactic radiosurgery (SRS) boost to a median dose of 12 Gy. After a median follow-up period of 19 months, a 76% survival rate was reported. Sarkaria et al<sup>58</sup> described 115 patients with high-grade glioma who received conformal radiation therapy and a SRS boost; median survival time was 96 weeks. These results called into question whether they represented a benefit from SRS or simply selection bias.

RTOG 93-05 compared conformal irradiation plus carmustine with or without a SRS boost for newly diagnosed GBM. No differences were observed in terms of OS (median, approximately 13 months in each arm) or quality of life.<sup>59</sup>

SRS may still have a role in the treatment of recurrent disease, particularly if a focal region of recurrence can be defined.<sup>63</sup> However, this has not been tested in prospective trials.

### Brachytherapy

Brachytherapy, the use of implanted radioactive material at the site of the tumor offers a mechanism for focal dose escalation. Both permanent and temporary radioactive implants have been used. Early positive results by Gutin et al<sup>60</sup> suggested a potential survival benefit in a Phase II trial. These findings were not reproduced in subsequent randomized trials.<sup>61,62</sup>

Interest in this modality was rekindled when the GliaSite radiation therapy system (Proxima Therapeutics, Alpharetta, Georgia) received approval by the Food and Drug Administration (FDA) in 2001. This intracavitary device is implanted at the time of tumor debulking, and a solution of iodine-125 (<sup>125</sup>I) is injected into an expandable closed-catheter balloon. A retrospective study suggested reasonable safety and promising efficacy.<sup>63</sup> A Phase I study was conducted.<sup>64</sup> However, the implant induces changes in imaging that complicate determination of disease progression.<sup>65</sup>

### Chemotherapy: Concurrent with EBRT, Maintenance, and Other

Early randomized trials of chemotherapy were individually negative, but meta-analysis of these trials showed that 15% to 20% of patients treated with radiation therapy (RT) and nitrosoureas survived at least 18 months versus 5% treated with radiotherapy alone (Table 27-1).<sup>37,38,66,67</sup> Nitrosoureas, especially carmustine, were the most commonly used drugs, although procarbazine was also used extensively.<sup>68</sup> The combination of procarbazine, lomustine (CCNU), and vincristine (PCV)<sup>69</sup> had no clear benefit (yet much greater toxicity) versus carmustine for anaplastic astrocytoma,<sup>70</sup> and this regimen has been largely abandoned for nonoligodendroglial tumors.

Intratumoral delivery of chemotherapy for residual postoperative disease is most commonly in the form of carmustine-eluting (Gliadel) wafers. Patients undergoing wafer implantation during surgery for recurrent GBM survived approximately 2 months longer than patients without wafers in one study ( $p = 0.02$ ).<sup>71</sup> Treatment of newly diagnosed disease also yielded a 2-month prolongation of average survival.<sup>72,73</sup> However, this was not statistically significant when the analysis was restricted to patients with GBM histology. Of note, wafer delivery of carmustine versus systemic administration has not been compared for safety or efficacy. Gliadel does, however, carry an FDA label for implantation during resection of recurrent GBM and newly diagnosed malignant glioma. Attempts to treat residual visible or microscopic disease with other local chemotherapies delivered through implanted catheters and using convection-enhanced migration of drug have generally failed.<sup>74</sup>

Currently, the most widely used chemotherapeutic agent is temozolomide. Whether it is more effective than nitrosoureas has not been investigated, but it is unquestionably better tolerated with significant myelosuppression in less than 20% of patients.<sup>39,40</sup> Temozolomide was first approved for use in the United States in recurrent anaplastic astrocytomas following a phase II study.<sup>75</sup> A randomized study also demonstrated superior efficacy to procarbazine in recurrent GBM.<sup>76</sup>

Temozolomide for newly diagnosed GBM has been studied both when given before RT<sup>77</sup> and when combined with RT in various dosing schedules.<sup>78,79</sup> Its role for newly diagnosed GBM was established by Stupp et al<sup>39,40</sup> on the basis of the EORTC 26981/22981 and NCIC CE.3 trial (Figure 27-4). In



this Phase III multicenter study, 573 patients with newly diagnosed GBM received RT alone or RT with concurrent temozolomide followed by six adjuvant cycles of temozolomide. The patients who received the combined-modality regimen had significantly longer OS and PFS without significantly more toxicity (Table 27-1). The 5-year OS was 10% among those receiving temozolomide versus 2% among those receiving RT alone ( $p < 0.0001$ ).<sup>39</sup> Patients in the most favorable RPA class had a 5-year OS rate of 28% following combined therapy.<sup>39</sup> In a companion paper, Hegi et al<sup>41</sup> reported that methylation of the promoter for the O<sub>6</sub>-methylguanine DNA methyltransferase (*MGMT*) gene, which encodes the DNA repair enzyme O<sub>6</sub>-alkylguanine DNA alkyltransferase (AGT or AGAT, but now commonly also referred to as *MGMT*), was correlated with prolonged survival and patients with *MGMT* methylated tumors benefited the most from temozolomide.

*MGMT* repairs DNA damage induced by temozolomide, and methylation of the *MGMT* promoter silences expression of the protein, thereby accentuating the antineoplastic effects of temozolomide. However, the mechanism by which *MGMT* promoter methylation leads to an improved outcome is more complex. For example, some patients with tumors that did not demonstrate *MGMT* methylation also benefited from temozolomide although it is increasingly recognized that the initial test probably scored some “methylated” tumors as either “unmethylated” or “unknown.”<sup>39,41</sup> Accordingly, it remains unclear whether *MGMT* analysis should categorically alter treatment, although this situation remains somewhat fluid. In addition, patients with tumors harboring methylated *MGMT* survived longer following treatment with RT alone than patients who did not have tumors harboring methylated *MGMT* treated identically.<sup>39,40</sup> Others reported similar findings in GBM<sup>80</sup> and other malignant gliomas.<sup>81</sup> Moreover, *MGMT* protein expression by immunostaining does not predict outcome.<sup>82</sup>

Several groups have explored intensifying the temozolomide dosing schedule in an attempt to overcome *MGMT*-mediated resistance.<sup>83,84</sup> The intensified regimens are designed to deplete *MGMT* activity as suggested by previous studies.<sup>85</sup> RTOG 0525 was a Phase III randomized placebo controlled study that compared standard temozolomide dosing following completion of radiotherapy (150 mg/m<sup>2</sup> to 200 mg/m<sup>2</sup> body surface area days 1 to 5 of 28) versus an intensified regimen (75 mg/m<sup>2</sup> to 100 mg/m<sup>2</sup> body surface area days 1 to 21 of 28). This prospectively validated that *MGMT* promoter methylation is a favorable prognostic factor regardless of treatment.<sup>86</sup> However, “dose-dense” temozolomide was more toxic than standard dosing and did not significantly alter PFS or OS regardless of *MGMT* status.<sup>86</sup>

Therefore, *MGMT* promoter methylation is prognostic but the mechanism remains unclear. In addition, there are now several different methodologies to test for *MGMT* promoter methylation, which may lead to discordant results.<sup>87</sup> It is possible that *MGMT* is a marker of more global hypermethylation and is only one of multiple genes mechanistically involved in resistance to alkylator chemotherapy and prognosis in tumors harboring the recently described Glioma CpG island methylator phenotype (G-CIMP).<sup>88,89</sup>

Another major area of investigation has been the use of vascular endothelial growth factor receptor (VEGFR) signaling inhibitors. Bevacizumab (Avastin) is a monoclonal antibody against VEGF that competitively inhibits binding of the ligand to VEGFR and targets tumor vascularity. It is the most widely studied of these antiangiogenic strategies.

Based on encouraging response rates and prolongation of PFS in recurrent GBM, two major Phase III studies, RTOG 0825 and Avastin in Glioblastoma (AVAglio) sponsored by F. Hoffmann La Roche, were launched nearly simultaneously.

Following maximal safe surgical resection, both randomized patients to receive RT and temozolomide plus either bevacizumab or placebo. Although there were subtle differences in trial design with respect to extent of resection (e.g., biopsy-only patients not permitted in RTOG 0825 but allowed in AVAglio, timing of treatment, etc.), both demonstrated prolongation of PFS (median 10.7 versus 7.3 months,  $p = 0.007$  for RTOG 0825; median 8.4 versus 4.3 months,  $p < 0.001$  for AVAglio).<sup>90,91</sup> However, neither demonstrated a difference in OS (median 15.7 versus 16.1 months,  $p = 0.21$  for RTOG 0825; median 16.8 months versus 16.7 months for AVAglio,  $p = 0.10$ ). Both permitted cross-over from placebo to bevacizumab that was offered as part of the study design to participants in RTOG 0825 and permitted but not offered routinely in AVAglio.

These results have not categorically settled the issue of whether bevacizumab should be used for newly diagnosed GBM. In RTOG 0825, the prolongation of PFS did not meet the prespecified statistical level (30% reduction in hazard,  $p = 0.004$  required for significance), whereas it did for AVAglio (23% improvement,  $p = 0.01$  required for significant difference in PFS). In addition, quality of life measures in RTOG 0825 did not demonstrate a “Net Clinical Benefit,” in fact it was worse for those who received bevacizumab, whereas improvement was observed in AVAglio.<sup>90,91</sup> In the context of these results, some practitioners consider using bevacizumab for patients with unresectable large deep tumors with surrounding edema, and especially patients with poor performance status, but such patients would have been excluded from the Phase III trials.

Other antiangiogenic therapies also have not improved survival. For example, the EORTC in collaboration with the Canadian Brain Tumor Consortium conducted the Phase III CENTRIC (Cilengitide in combination with Temozolomide and Radiotherapy In newly diagnosed glioblastoma Phase III randomized Clinical trial) study to evaluate the integrin inhibitor cilengitide that has reported antiangiogenic properties.<sup>92</sup> Based on encouraging Phase II results among the subset of patients with *MGMT* methylated tumors,<sup>93</sup> CENTRIC randomized such patients with newly diagnosed GBM to standard RT and temozolomide with or without cilengitide.<sup>94</sup> Median survival was unchanged (26.3 months in both arms, hazard ratio [HR] 1.02,  $p = 0.86$ ).<sup>94</sup> There was also no significant improvement in PFS (13.5 months versus 10.7 months, HR 0.93,  $p = 0.48$ ) as evaluated by the treating investigator.<sup>94</sup> A study of cediranib for newly diagnosed GBM (RTOG 0837) is ongoing; however, the failure of cediranib to demonstrate meaningful efficacy in recurrent GBM is concerning.

Two studies have evaluated antiangiogenic therapy in particular for patients with *MGMT* unmethylated tumors. The ongoing CORE (Cilengitide in patients with newly diagnosed glioblastoma multiforme and unmethylated *MGMT* gene promoter) randomized such patients to RT and temozolomide with or without cilengitide. Results are not available yet. The German GLARIUS Phase II trial randomized cases with unmethylated *MGMT* 2:1 to RT and concurrent bevacizumab followed by maintenance temozolomide for six cycles.<sup>95</sup> The primary endpoint was 6-month PFS determined by central review (generally considered somewhat unconventional), with 80% power to detect an increase from 40% to 60%. Results favored the bevacizumab arm (79.6% versus 41.3%,  $p < 0.0001$ ). Median PFS (9.7 versus 6.0 months, HR 0.3,  $p < 0.0001$ ) and OS (16.6 versus 14.8 months, HR 0.60,  $p = 0.031$ ) also significantly favored the experimental arm.<sup>95</sup> These results require maturation and further validation, but begin to suggest a subgroup of patients who may benefit from addition of bevacizumab containing chemotherapy in lieu of temozolomide for newly diagnosed GBM. Notably, OS did not favor the bevacizumab group in RTOG 0825 or AVAglio,<sup>90,91</sup> but these trials were not intended for comparison.



## Anaplastic Gliomas

Anaplastic astrocytomas, anaplastic oligodendrogliomas, and anaplastic oligoastrocytomas represent the most common WHO grade III tumors.<sup>1,21</sup> In anaplastic gliomas, resection appears to improve survival relative to biopsy, as it does for GBM.

### Anaplastic Astrocytic Neoplasms

It is generally accepted that RT should be administered postoperatively for astrocytomas. In a German study (NOA-04), early analysis demonstrated that survival was equivalent whether chemotherapy or RT was used first among patients with anaplastic astrocytomas, oligodendrogliomas, and mixed tumors.<sup>12</sup> However, time to progression following RT was longer than after chemotherapy, and initial radiation therapy achieved more complete and partial responses than initial chemotherapy, suggesting the superiority of RT.<sup>96</sup> In addition, the data were relatively immature at initial publication, and longer follow-up may demonstrate the importance of primary RT more fully among anaplastic astrocytomas, or mixed oligoastrocytomas without 1p19q codeletion.

Regarding chemotherapy, Combs et al<sup>97</sup> reviewed the outcome of 191 patients with grade III astrocytic tumors treated at the University of Heidelberg with either RT alone or RT in combination with temozolomide during a 20-year period (from 1988 to 2007). In this retrospective study, no significant advantage in rates of OS or PFS could be attributed to the combination. RTOG trial 9813 randomized patients with anaplastic astrocytomas (or oligoastrocytomas) to RT with concurrent nitrosourea (carmustine or lomustine) or with temozolomide, and results are pending.

The ongoing Concurrent vs. Adjuvant Temozolomide for NON 1p19q co-deleted anaplastic gliomas, also called EORTC 26053-22054 (CATNON) Intergroup trial randomizes patients to receive postoperative RT alone, concurrent temozolomide and RT without adjuvant temozolomide, RT (without concurrent temozolomide) followed by adjuvant temozolomide, or RT with both concurrent and adjuvant temozolomide (Figure 27-5). Although technically this study allows any WHO grade III glioma without 1p/19q codeletion, the majority of the tumors will be anaplastic astrocytomas.

### Anaplastic Oligodendroglial Tumors

Long-term follow-up is now available for patients enrolled on RTOG 94-02<sup>10,98</sup> and EORTC 26951.<sup>11,99</sup> In these studies, radiation was compared to radiation with PCV chemotherapy. The RTOG trial entailed administration of chemotherapy before irradiation (intensified PCV<sup>100</sup> for up to four cycles in the combined-modality arm) whereas the reverse sequence (i.e., RT alone versus 59.4 Gy followed by up to six cycles of standard dose PCV) was used in the EORTC trial. With median

follow-up in excess of 10 years in both studies, there was a dramatic improvement in OS associated with combined chemotherapy and radiotherapy (irrespective of sequence) among patients with anaplastic oligodendroglioma or anaplastic mixed oligoastrocytoma whose tumors contain allelic loss of chromosomes 1p and 19q, compared with radiation alone. For example, in RTOG 9402, median survival was 14.7 years versus 7.3 years ( $p = 0.03$ , HR 0.59 for chemoradiotherapy) and in EORTC 26951 median survival was not reached versus 9.3 years ( $p = 0.0594$ , HR 0.56 for chemoradiotherapy). In addition, patients with *IDH* mutant but not 1p19q codeleted tumors also benefited from chemotherapy, although the magnitude was lower than for those with tumors that harbored both codeletion and *IDH* mutation.<sup>101</sup> Those with *MGMT* promoter methylation<sup>87</sup> or *ATRX* expression<sup>101</sup> may also benefit regardless of 1p19q deletion status.

The applicability of these findings in an era where PCV is no longer popular remains debatable, especially because temozolomide has almost entirely replaced PCV in routine practice<sup>102</sup> despite the lack of a clear efficacy equivalence. What is clear, however, is that RT alone is inadequate for treatment of patients with codeleted tumors, and likely those with *IDH1* or *IDH2* mutated tumors, regardless of deletion status.

In addition, the role of RT for newly diagnosed anaplastic oligodendroglioma is becoming the subject of controversy because of the tumor's reported sensitivity to chemotherapy,<sup>100</sup> especially tumors with 1p/19q codeletion.<sup>103</sup> Neither RTOG 9402 nor EORTC 26951 used chemotherapy alone, which was recommended by 42% of clinicians (typically with temozolomide)<sup>13</sup> and used in 55% of patients from 2005 to 2007 in a retrospective series of codeleted tumors, without prospective data supporting such usage.<sup>102</sup> The ongoing CODEL (for 1p/19q CO-DEleted tumors) trial now randomizes patients to RT followed by PCV versus RT plus concurrent and adjuvant temozolomide, versus temozolomide alone (Figure 27-6).

The CATNON and CODEL study designs are premised on the belief that the 1p/19q chromosomal status may be more important than the histologic subtype for WHO grade III lesions. However, scientific advances in the interim may outpace the questions posed by these trials as it becomes apparent that *MGMT* promoter methylation<sup>81,87</sup> and *IDH* gene mutation<sup>12,18,101</sup> are also powerful markers of outcome in anaplastic gliomas. There is a clear need to move beyond histologic information (e.g., WHO subtyping) because important advances in prognostication have been made.<sup>104</sup>

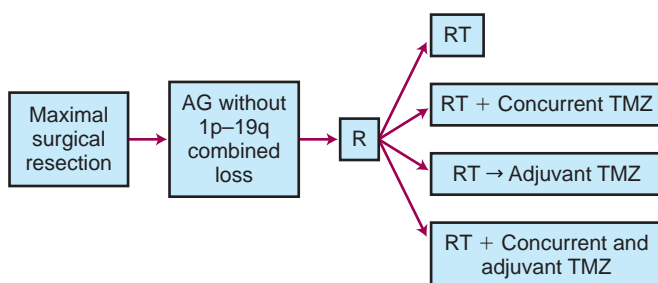
## Special Topics

### Toxicities of Radiation Therapy

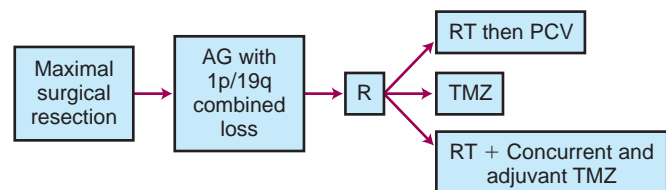
Acute and late effects of irradiation, including brain necrosis are discussed in a subsequent section on [Irradiation Techniques and Toxicities](#).<sup>45,97,105-107</sup>

### Elderly Patients with GBM

More than 44% of GBMs occur in patients older than 65 years of age,<sup>1</sup> but prospective trials often exclude elderly patients.<sup>39,40</sup>



**Figure 27-5** Schema from the CATNON study (Intergroup phase III, EORTC 26-53, RTOG 0834). AG, Anaplastic glioma; R, randomization; RT, radiotherapy; TMZ, temozolomide.



**Figure 27-6** Schema from the CODEL trial (NCCTG NO0557/RTOG 0670). PCV, Procarbazine; TMZ, temozolomide.



Because these patients often have a worse outcome than younger patients, there has been some uncertainty with regard to the aggressiveness of treatment, and the definition of “elderly” is highly variable.

A Finnish randomized study of 30 patients older than age 65 years with imaging consistent with malignant gliomas demonstrated longer median survival following craniotomy than following biopsy (5.7 versus 2.1 months;  $p = 0.035$ ).<sup>32</sup> The Association of French-Speaking Neuro-Oncologists<sup>106</sup> conducted a randomized trial comparing RT alone (50 Gy in conventional fractionation) versus supportive care among patients older than 70 years of age. The trial was discontinued after 85 patients were registered when it became apparent that RT was associated with a statistically advantageous outcome (median survival time, 29 versus 17 weeks;  $p = 0.002$ ).

Efforts to abbreviate the duration of RT have been conducted. For example, a randomized study in patients older than age 60 years demonstrated that 40 Gy in 15 fractions was not inferior to 60 Gy in 30 fractions.<sup>107</sup>

A Phase II study of temozolomide alone in 32 patients older than age 70 years with newly diagnosed GBM demonstrated a response rate of 31%, median PFS time of 5 months and median survival time of 6.4 months, comparable to RT alone.<sup>108,109</sup> A single-arm 77-patient Phase II study for those older than age 70 with poor performance status (Karnofsky Performance Status [KPS] <70)<sup>110</sup> demonstrated median survival of approximately 6 months, with 26% becoming functionally independent (KPS at least 70).<sup>111</sup> Among those with *MGMT*-promoter methylated tumors (13 of 31 tested) median OS was approximately 7 months, and *MGMT* status was a statistically significant prognostic factor.<sup>111</sup>

In the NOA-08 trial conducted by the German Neuro-Oncology Working Group,<sup>112</sup> 373 patients older than age 65 with KPS of at least 60 with anaplastic astrocytoma or GBM (in 89%) were treated following randomization with RT (60 Gy) or an intensive schedule of temozolomide (100 mg/m<sup>2</sup> days 1 to 7 and 15 to 21 of every 28) without RT. If patients did not tolerate treatment or if they demonstrated progression, then cross-over (or surgical intervention) was triggered. Survival was slightly shorter following chemotherapy alone (8.6 months versus 9.6 months), but did not reach the prespecified statistical endpoint for declaring it inferiority (i.e., it was non-inferior, based on accepting a certain level of survival loss designated as “noninferior”). Among patients with *MGMT* unmethylated tumors, RT was statistically superior (4.6-month versus 3.3-month event-free-survival). In addition, in *MGMT*-methylated cases, treatment with temozolomide was superior (8.4-month versus 4.6-month event-free survival). Analyzed differently, *MGMT* status did not influence event-free survival following RT (4.6 months regardless of *MGMT* status). However, *MGMT* status clearly and strongly influenced event-free survival following temozolomide alone (8.4 months versus 3.3 months for methylated versus unmethylated). Accordingly, among those with *MGMT*-methylated tumors, RT alone was an inferior treatment to temozolomide, and similarly, temozolomide alone was an inferior treatment to RT in those with unmethylated tumors. Many have presumed by implication that temozolomide in lieu of RT could be considered a reasonable treatment strategy in the elderly, but this supposition does not take into account the fact that results with combination RT and temozolomide are superior in almost all trials, and in the U.S. trials, even patients in their 80s were enrolled. Accordingly, monotherapy should be reserved for patients with poor KPS. Further, the intense schedule of temozolomide was excessively toxic and more standard schedules of temozolomide, commonly used in the United States were not studied in this trial,<sup>112,113</sup> and as eluded to previously, the combination of RT and temozolomide (the

standard of care for patients younger than age 70 in Europe, and no age limit imposed in U.S. clinical trials, including enrollment patients, even in their 80s, as long as KPS was >70)<sup>39,40</sup> was not studied. It must further be underscored that NOA-08 had a noninferiority design, which included a definition of inferiority of temozolomide as a greater than 25% difference in survival endpoints, which arguably represents too much latitude and insufficient statistical rigor to allow clinicians to conclude that a new standard of care has emerged, especially given that there are few other comparable scenarios in oncology, where 25% loss of survival is accepted as noninferior.

In a Phase III trial from the Nordic Clinical Brain Tumour Study Group, 291 patients were randomized to standard dose temozolomide, standard (60 Gy) RT, or hypofractionated RT (10 fractions of 3.4 Gy each), and similar to the NOA-08 trial, there was no combined-modality therapy arm.<sup>114</sup> The trial has been criticized for its inclusion criteria of 60-year-olds under the rubric of “elderly” in view of the fact that the median age for the diagnosis of GBM is closer to 65 in the contemporary era.<sup>115</sup> Nonetheless, in an unplanned posthoc subset analysis of patients older than 70 years of age ( $n = 123$ ), standard irradiation was associated with inferior survival in comparison to the other therapeutic arms; there was no difference in outcome between temozolomide and short-course RT, with fewer cytopenic toxicities in the short-course RT arm. The Nordic trial, much like the German study, revealed that *MGMT*-promoter methylation predicted for better outcomes in those treated with temozolomide alone, and once again it must be noted that the trial was not initially powered for this assessment as a primary observation. These trials are still open to interpretation at this juncture. The case could be made that for those patients in whom for reasons of poor performance status or inability to commute for long-course RT, temozolomide alone or short-course RT without temozolomide is an acceptable alternative; for patients who might be at higher risk of infection, short-course RT would induce fewer cytopenic episodes and might actually be preferred over temozolomide. For *MGMT*-methylated tumors in patients for whom daily radiation treatments for 6 weeks or so may impose unacceptable burden, temozolomide alone could be considered. This is not to say that RT is not an effective option for elderly patients, especially for patients with unmethylated-promoter *MGMT*. Indeed, an important next step will be to investigate chemoradiation strategies using a shortened course of irradiation, especially in the elderly poor KPS subset of patients; this is the subject of an ongoing trial by the EORTC and NCI Canada (NCT00482677).

It should also be noted that intravenous temozolomide has recently become available as an option for elderly or otherwise impaired patients who cannot swallow capsules or comply with an oral regimen.<sup>116</sup>

### Pseudo-Progression

Pseudo-progression confounds interpretation of imaging performed in the first several months following completion of RT. Descriptions of “pseudo-progression” appeared as early as 1979, when Hoffman et al<sup>117</sup> described patients treated with RT and carmustine. Among patients thought to have experienced disease progression immediately following irradiation, nearly half were shown to have improvement or at least stabilization on subsequent brain imaging.

A report in 2004 described that approximately one third of patients with gliomas stabilized or improved with no change in management.<sup>118</sup> Chamberlain et al<sup>119</sup> reported histologically proven treatment injury rather than disease progression in approximately 50% of patients with symptomatic resectable lesions felt to represent worsening disease



following concurrent RT and temozolomide. The incidence of pseudo-progression has been reported to be as high as 75%, in selected subsets of patients with GBM.<sup>84,120,121</sup> Pseudo-progression rather than “true” progression may also correlate with *MGMT*-promoter methylation,<sup>120</sup> although this has not yet been prospectively validated.

Multiple imaging techniques have been explored to delineate radiographic pseudo-progression from true progression.<sup>120,122-126</sup> However, at this time, histologic analysis is the only validated method of distinguishing the two diagnoses, and even that has its limitations because of sampling issues, and difficulty in interpreting tumor cell viability posttreatment.<sup>127</sup>

It is presumed that the incidence of pseudo-progression is higher following concurrent RT and temozolomide than that following RT alone, although supportive evidence is equivocal.<sup>128</sup> As chemoradiotherapy is now the accepted standard of care for newly diagnosed GBM, no prospective study is likely to study this definitively. One approach to dealing with this issue involves using the MRI study done following RT as a new baseline, unless there is surgical documentation of recurrent disease or clear worsening outside of the RT portal. This remains an area of active study.<sup>129</sup> It is also worth noting that the “stabilization” of the peritumoral vasculature induced by antiangiogenic agents can possibly lead to a reduction in the pseudo-progression event rate, and has sometimes been used to manage florid imaging changes, with or without clinical deterioration.

## RECURRENT DISEASE

### Chemotherapy

Efforts to treat recurrent disease with single agents, either cytotoxics or molecular-targeted agents, have generally been unsuccessful, at least in part because of the innate resistance, poor drug penetrability, and molecular complexity of the disease.<sup>130</sup> Some studies suggest the key may lie in identifying the patients most likely to respond based on molecular profiling of tumor tissue at recurrence.<sup>131</sup>

An exception is the use of agents that target vascular endothelial growth factor (VEGF) or VEGFRs. Bevacizumab, a monoclonal antibody against VEGF, is the most widely studied of these antiangiogenic strategies.

The “BRAIN” trial was a noncomparative Phase II study for recurrent GBM that randomized 167 patients to either bevacizumab alone or bevacizumab combined with irinotecan,<sup>132</sup> the latter regimen adopted from activity of that combination in colon cancer.<sup>133</sup> The 6-month PFS was 43% with bevacizumab and 50% with bevacizumab plus irinotecan.<sup>132</sup> Similar results were seen in a single-arm Phase II study conducted by the NCI.<sup>134</sup> None of these trials however provided categorical evidence of improved OS.

These results are far superior to those of prior available therapies. For example, the 6-month PFS following carmustine is approximately 15% to 20%.<sup>135</sup> Emerging data from the randomized Dutch BELOB (BEvacizumab vs. LOMustine in glioblastoma, Or Both) study demonstrate the superiority of bevacizumab (10 mg/kg days 1 and 15 of 28) combined with lomustine (90 mg/m<sup>2</sup> to 110 mg/m<sup>2</sup> every 6 weeks) versus either alone in terms of 6-month PFS (16% for bevacizumab, 13% for lomustine alone, >40% for lomustine with bevacizumab).<sup>136</sup> Based on these results, EORTC 26101 has been redesigned to compare lomustine alone (110 mg/m<sup>2</sup>) versus bevacizumab with lomustine (90 mg/m<sup>2</sup>), specifically seeking a survival benefit in a Phase III context for recurrent GBM.

Trials of other VEGF/VEGFR inhibitors have been negative. For example, REGAL (Recentin in Glioblastoma Alone

and With Lomustine) was a Phase III trial<sup>137</sup> that tested efficacy of Recentin (cediranib), a direct oral pan-VEGFR inhibitor after a prior promising Phase II study.<sup>138</sup> An interim analysis demonstrated median PFS was longer following cediranib (92 days) or cediranib and lomustine (125 days) than lomustine (plus placebo, 82 days). However, median OS was not longer with cediranib (8.0 months versus 9.4 months versus 9.8 months), and the PFS benefit did not reach the prespecified improvement goal; accordingly, the trial was declared negative and accrual terminated.<sup>137</sup>

Therefore, despite increased response rates and improved PFS, to date there are no data clearly demonstrating a survival advantage for the use of bevacizumab, and its major potential toxicities include thromboembolic disease, hemorrhagic consequences, and hypertension. In addition, almost all salvage treatments following progression on bevacizumab are ineffective,<sup>41,139</sup> and therefore, the timing of bevacizumab for either first or later recurrence remains controversial. Recent data suggest that deferring bevacizumab to a second or later recurrence does not shorten survival.<sup>140</sup> The potential toxicity, as well as the fear of inducing a more invasive tumor phenotype also tempers enthusiasm for use of this agent in newly diagnosed disease, especially in light of lack of survival benefit from the RTOG 0825<sup>90</sup> and AVAglio trials.<sup>91</sup>

### Alternating Electric Fields

Finally, one nonchemotherapy approach has been explored using alternating electric fields, tumor treatment fields (TTF) generated by a current source on the scalp (NovoTTF). This therapy is hypothesized to affect the mitotic spindle and thereby reduce proliferation. A Phase III trial suggested non-inferiority when compared to any one of several possible physician-chosen chemotherapy regimens (median survival 6.6 months versus 6.0 months, HR 0.86 [95% CI, 0.66 to 1.12],  $p = 0.27$ ; 6-month PFS 21.4% versus 15.1%,  $p = 0.13$ ) with less toxicity than chemotherapy.<sup>141</sup>

Favoring a role for the device in treatment of glioblastoma, in addition to the similarity of survival and fewer side effects, more responses were seen in the TTF arm, although the difference was not significant and the response rate was low regardless of treatment. These results led to accelerated FDA approval. It should also be noted that 31% of patients received bevacizumab as the comparator chemotherapy during treatment on study, and approximately 20% of patients in both arms had a bevacizumab refractory tumor, suggesting benefit of the device in such patients.

However, it should be noted the trial was formally negative. The primary endpoint was improvement in survival. The statistical design had 80% power to detect a 60% increase in survival (HR 0.63,  $p \leq 0.05$ ), and this was not achieved. The study was neither designed nor powered for a noninferiority endpoint, and the lack of a difference in survival in this study is not necessarily the same as true noninferiority.

In addition, the requirement for device approval is less stringent than for a drug, and the trial design and results have been heavily criticized. For example, there was no placebo device used as a control. One explanation is the questionable ethics of randomizing patients to no treatment whatsoever had the design been chemotherapy compared with NovoTTF compared with placebo device. However, that could have been ameliorated by randomizing patients to a specific chemotherapy (such as a nitrosourea or bevacizumab or both) in combination with either NovoTTF or placebo device.

Therefore, a clear interpretation remains elusive. The device appears reasonably safe, and it may well be that NovoTTF was noninferior to various chemotherapies. However, it is equally plausible that neither the device nor the chemotherapies were



beneficial to the patients. A Phase III study for newly diagnosed GBM (without placebo control) is ongoing, and a trial evaluating survival benefit in bevacizumab refractory GBM is being designed through the RTOG Foundation.

## Reirradiation

Focal RT approaches are often employed with limited volume recurrences. In a retrospective analysis of 95 patients with recurrent gliomas treated with the GlioSite device, the median survival time was 36 weeks.<sup>142,143</sup> However, whether this is a function of true benefit or patient selection has not been determined.

Fractionated RT to treat larger-volume recurrent disease has also been employed. Although there has been speculation from animal studies that neural tissue will recover from previous irradiation to a large extent once some time has elapsed (e.g., 1 year to 3 years),<sup>144</sup> no firm data quantify the degree to which one can assume that a “dose discount” exists. It is most likely that the damage from reirradiation is underestimated because the majority of patients do not live long enough to express such damage. A small study showed good short-term tolerance to intensity-modulated radiation therapy (IMRT) delivered in six daily fractions of 5 Gy each.<sup>145</sup> A recent single-arm trial from the Memorial Sloan Kettering Cancer Center (MSKCC) demonstrated reasonable safety and efficacy of combined bevacizumab and reirradiation using IMRT for small recurrent malignant gliomas.<sup>50</sup> No radionecrosis was observed and survival appeared to be prolonged relative to historic controls, suggesting that bevacizumab may not only treat radionecrosis<sup>146</sup> but might protect against it. Another approach was recently reported by investigators from Jefferson Medical College<sup>147</sup> who treated 147 patients with recurrent high-grade glioma to 35 Gy in 3.5-Gy fractions with stereotactic radiation therapy. This hypofractionated stereotactic radiation therapy (HSRT) approach was associated with a median survival time in excess of 10 months.

Based on the promising results from the MSKCC and Jefferson trials, RTOG 12-05 was recently opened for patients with recurrent GBM. The Phase II study, which will enroll approximately 180 patients who are bevacizumab-naïve with recurrent disease, compares concurrent bevacizumab plus reirradiation (using a hypofractionated RT schema of 35 Gy in 10 fractions) to bevacizumab alone.

## IRRADIATION TECHNIQUES AND TOXICITIES

Whole-brain radiation therapy (WBRT) has been replaced with partial brain techniques by consensus for almost all gliomas. Although the dose computation component of treatment planning requires CT imaging, effective image registration with MRI has made this the modality of choice for contouring. The notion of a dedicated MRI simulator has also been proposed as a valuable adjunct in the radiotherapeutic management of high-grade gliomas.<sup>148</sup> However, treatment plans based only on MRI are not able to take into account tissue electron-density variations, which may lead to slightly inaccurate dose calculations.

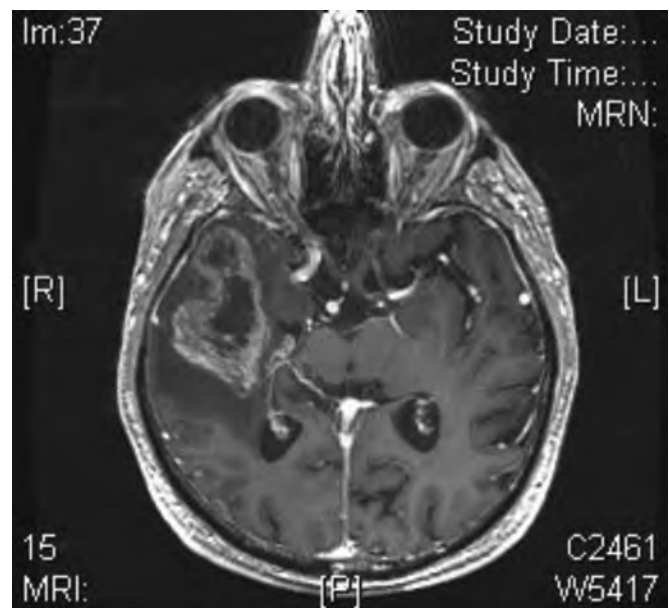
Patients are usually simulated after surgical wound apposition is reasonably stable and free of infection (generally, 10 days to 14 days after the operation). An immobilization mask is fashioned to reduce motion during and between fractions. The planning CT scan is extended to encompass the head and neck region to allow sufficient anatomic areas for proper image fusion and generation of high-quality digitally reconstructed radiographs (DRRs) and to permit the introduction

of noncoplanar beams; ideally, the slice thickness should match that of the MRI used for fusion.

For high-grade gliomas, especially GBM, T1 contrast-enhanced sequences are used to define the gross tumor volume (GTV) and the T2 or FLAIR sequences plus a margin define the microscopic disease extent, or clinical target volume (CTV), which reflects the bulk of microscopic infiltration. To arrive at a planning target volume (PTV), both organ motion and setup error must be taken into account. Organ motion in the brain is quite minimal during therapy (e.g., <1 mm). The PTV may be further modified to exclude normal tissue in areas where gliomas are unlikely to infiltrate. Bokstein et al<sup>149</sup> recently demonstrated that when anatomic barriers such as the temporal bone can serve as a border to impede tumor spread, failure is likely to be seen in less than 5% of cases even when the customary 2-cm margins are *not added* to the abnormalities seen on MRI (Figure 27-7).

In general, there are two major schools of thought (with numerous institutional variations based on these) that provide guidance for the prescription of the radiation regimen. The RTOG approach is a biphasic technique that includes an initial PTV (PTV 1) followed by a second PTV (PTV 2) that represents the cone down. In the lexicon of the RTOG, the PTV 1 includes the T2 or FLAIR CTV with a margin and is treated to 46 Gy in 2-Gy fractions. The PTV 2 includes the T1-enhancing GTV with a margin and is treated to an additional 14 Gy. The EORTC recommends a single-phase technique using one treatment volume throughout the course of therapy. Table 27-2 shows the partial brain volumes advocated by several cooperative groups for the successive phases of partial brain irradiation.

With the advent of functional imaging tools (e.g., functional MRI [fMRI]) it may be possible to specifically modify irradiation doses to functional brain areas. Figure 27-8 displays a treatment plan wherein the region governing motor control (e.g., finger tapping) is delineated to enable an accounting for dose deposition. In this case, this region in the right hemisphere (i.e., governing tapping by the left upper extremity) is included in the high-dose region but the contralateral side is well spared; a major caveat here is that the dose-response relationships for various functional subvolumes in the brain are largely unknown, and therefore, this



**Figure 27-7** Lesion that could be treated without a full complement of margins because of anatomic barrier of the temporal bone.



information is of little practical dosimetric usefulness at this point in time.

In RTOG 08-25, it was noteworthy that approximately 80% of patients, irrespective of treatment arm, received IMRT. Lorentini et al<sup>150</sup> performed meticulous comparison of IMRT and three-dimensional (3D) conformal irradiation among patients treated for GBM. The IMRT plans consistently provided better target coverage than their 3D-conformal counterparts and yielded a statistically significant dose reduction to the healthy brain. The authors suggested that IMRT represents the superior technique when there are more than two regions of overlap between organs at risk (OAR) and the PTV.

Table 27-3 summarizes the tolerance of various OAR according to the new Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) guidelines. Lawrence et al<sup>151</sup> postulated that the original estimates of Emami et al,<sup>152</sup>

TABLE 27-2 Radiotherapy Volume Used in Current Clinical Trials		
RT Dose	Block Edge Dosimetry Margin*	Source for RT Dose
46 Gy	T2 + 2 cm	RTOG
14 Gy	T1 + 2.5 cm	
60 Gy†	T1 + 2-3 cm	EORTC
50 Gy	T2 + 2 cm	NCCTG
10 Gy	T1 + 2 cm	

3D, Three-dimensional; EORTC, European Organization for Research and Treatment of Cancer; Gy, Gray; NCCTG, North Central Cancer Treatment Group; RT, irradiation dose; RTOG, Radiation Therapy Oncology Group.  
 \*Both RTOG and EORTC prescribe dose to block edge (geometric) margin, whereas NCCTG prescribes dose to dosimetry (3D) margin.  
 †CENTRIC studies: either RTOG or EORTC volumes and RT doses are used, at individual physician discretion.

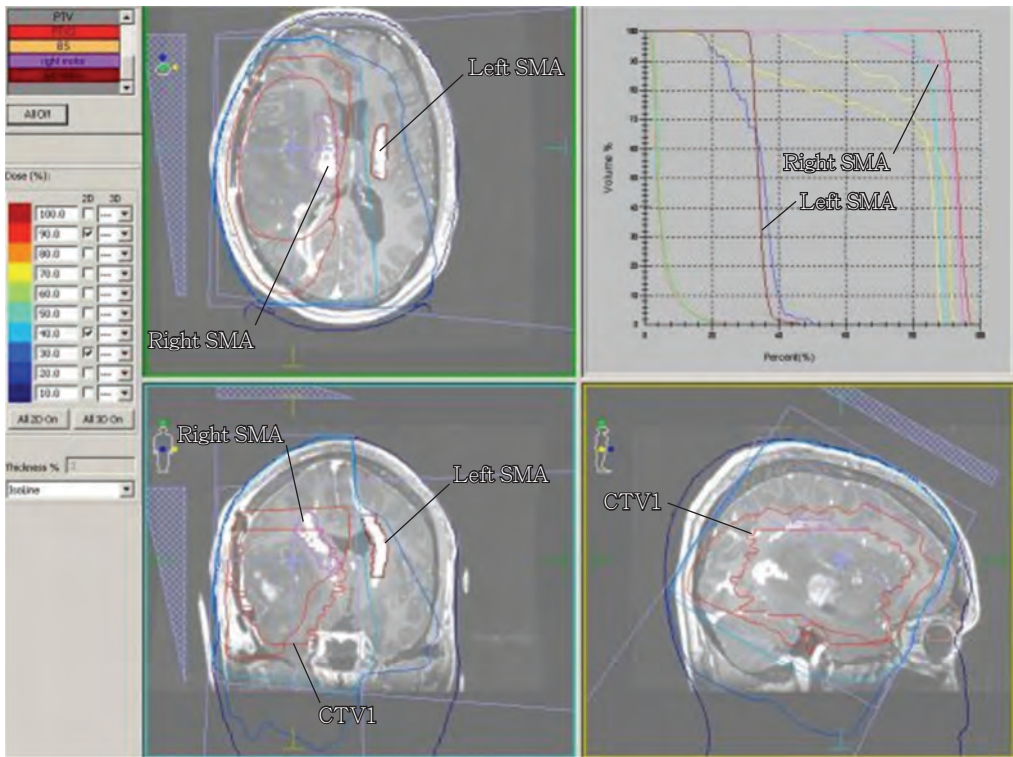
suggesting a 5% risk of chronic brain damage at 5 years when one third of the brain is irradiated to 60 Gy, were overly conservative. Instead, they hypothesized (Figure 27-9) that the dose correlated with a 5% risk of damage at 5 years following conventionally fractionated irradiation to the partial brain is 72 Gy, but data regarding subvolume and substructure sensitivity are not included in the QUANTEC assessment.

There may sometimes be a tendency to overlook structures that, if damaged, would have led to noncatastrophic sequelae. For instance, although it is true that radiation-induced cataracts are easily repairable,<sup>156</sup> avoidance of entrance and exit dose to the eye may be a relatively simple means of preventing not only cataracts but also conjunctivitis and a dry eye, by sparing the lacrimal gland. Similarly, when one contours the ear canals, there is now a greater awareness of the risks of developing otitis externa as well as otitis media.

There are reports of cytopenias arising from cranial irradiation even among patients who have not received chemotherapy.<sup>157</sup> The hypothesized mechanism of this is either irradiation of circulating blood within the radiation portals, injury to marrow in the cranium, or the use of vertex beams that exit through the spinal axis. The latter mechanism has also been invoked to explain radiation-induced fatigue by some investigators.<sup>158</sup>

For tumors located in the temporal lobes, the exit dose to the parotid gland may cause xerostomia. Tumors in such locations may be best treated with IMRT because one of the success stories of the application of IMRT to the head and neck region is indeed the elimination of this bothersome side effect.

Overall, the aim is to achieve the treatment plan that most closely approximates the defined volumes and thereby produces the most conformal plans. Relatively low energy beams (e.g., 6 MV) are typically employed. In contrast to the irradiation of varying organs containing primary tumors, it is

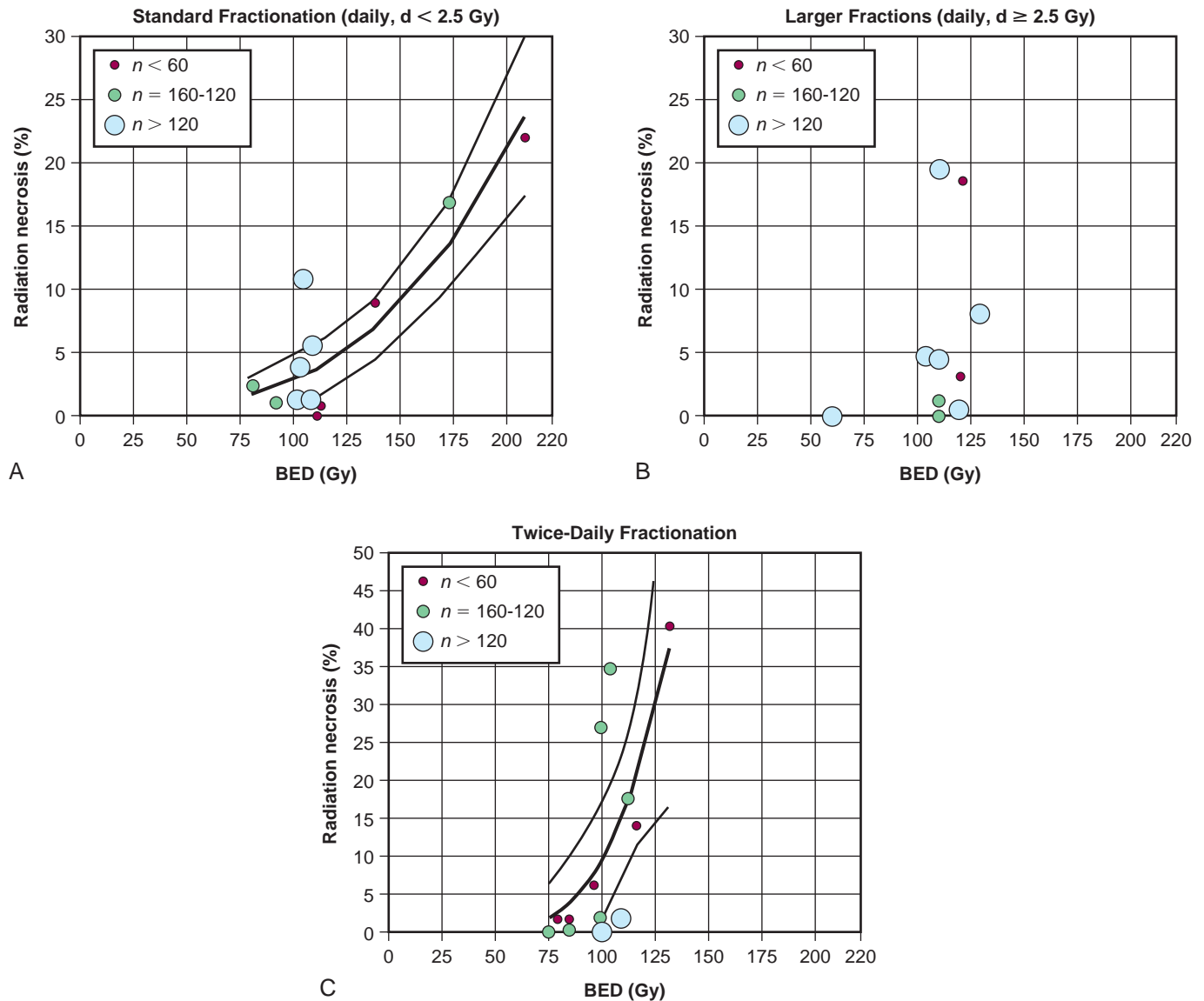


**Figure 27-8** Treatment planning based on a functional MRI. Note delineation of the clinical target volume (CTV) as well as left and right somatomotor areas (SMA) controlling hand movements of the right and left upper extremities, respectively.



**TABLE 27-3** Selected Organs at Risk for Treatment Planning of Malignant Glioma

Organ	Dose Limit	Comments
Brain parenchyma <sup>151</sup>	72 Gy	Brain appears to be more sensitive to fraction size > 2 Gy and to twice-daily radiation therapy
Optic apparatus <sup>153</sup>	60 Gy	12 Gy for single-fraction radiosurgery
Brainstem <sup>154</sup>	54 Gy	59 Gy if small volumes (i.e., 1-10 mL)
Parotid gland <sup>155</sup>	20 Gy	Severe xerostomia vis-à-vis sparing of one parotid gland
	25 Gy	Severe xerostomia vis-à-vis sparing of both parotid glands



**Figure 27-9** QUANTEC data for central nervous system tolerance based on the study in Lawrence et al. Relationship between biologically effective dose (BED) and radiation necrosis after fractionated radiotherapy. The Lawrence figure was done with a nonlinear least-squares algorithm using MatLab software (MathWorks, Natick, Mass.). The nonlinear function chosen was the probit model (similar functional form to the Lyman model). Dotted lines represent 95% confidence levels; each dot represents data from a specific study (Lawrence Table 2);  $n$  = patient numbers as shown. **A**, Fraction size less than 2.5 Gy. **B**, Fraction size 2.5 Gy or larger (data too scattered to allow plotting of “best-fit” line). **C**, Twice-daily radiotherapy. Redrawn with permission from Lawrence YR, Li XA, Naqa I, et al: Radiation dose-volume effects in the brain. *Int J Radiat Oncol Biol Phys* 76:S20–S27, 2010.



impossible to recommend a single idealized beam arrangement for high-grade gliomas. In this context, the role of proton therapy is being explored to further reduce dose to surrounding tissue distal to the tumor.

### Miscellaneous Technique Issues

Despite the absence of level I evidence, IMRT is increasingly used, sometimes to escalate the dose and at other times to spare surrounding tissues or to explore the concomitant boost concept. However, clinical data supporting improved outcomes from IMRT in high-grade gliomas are essentially nonexistent.

Guidelines for tumor delineation and dose selection for WHO grade III gliomas are less well developed. In general, the FLAIR and T2 compartments are regarded as containing microscopic disease and therefore constitute the CTV. The typical dose is 59.4 Gy or 60 Gy in 1.8-Gy to 2-Gy fractions.

### Toxicities of Radiation Therapy

Acute radiation morbidity includes fatigue, erythema, alopecia, headache, and rarely, nausea with or without vomiting; these are generally not severe and are usually self-limiting.<sup>45</sup> Some have cautioned that the combination of cranial RT and phenytoin as well as other anticonvulsants could give rise to the Stevens-Johnson syndrome,<sup>159,160</sup> but this dermatologic emergency is an exceedingly rare event, and the causal association between the two has not been established.

Late effects of radiation (e.g., somnolence and, especially, cognitive impairments) are more worrisome and may become manifest many years later.<sup>161</sup> The impact of partial brain irradiation on neurocognitive decline continues to be a hotly debated topic. The confounding factor is always the extent to which there is baseline cognitive impairment or decreased mentation secondary to tumor. Hippocampal sparing may emerge as a method to reduce the risks of neurocognitive injury as it appears to do in the treatment of brain metastases with WBRT.<sup>162</sup>

Brain necrosis is a serious and uncommon late toxicity, and recently bevacizumab has been explored as a treatment.<sup>146</sup> In a small trial, all patients showed improvement of MRI abnormalities as well as a reduction in corticosteroid requirements following treatment with bevacizumab.<sup>163</sup>

We currently estimate the risk of normal tissue damage based on the most sensitive 5% of the population. Accordingly, we bias our recommendations in a manner that is not germane to most individuals, and preliminary efforts at predicting the likelihood of toxicities based on risk are ongoing.<sup>164,165</sup>

## TREATMENT ALGORITHM, CONTROVERSIES, CHALLENGES, AND FUTURE POSSIBILITIES

### Treatment Algorithm

For adults up to age 70 years with newly diagnosed GBM, the current standard of care is safe maximal surgical resection (with or without Gliadel wafer implantation) followed by concurrent EBRT (approximately 60 Gy in 30 fractions) with temozolomide and followed by at least 6 months of adjuvant temozolomide (Figure 27-4). For suspected progression that occurs within 3 months of completing RT, the possibility of pseudo-progression should be strongly considered.<sup>166</sup> Relapsed disease may be treated with re-resection, second-line chemotherapy, or experimental therapy in a clinical trial. Reirradiation is also a possibility but is used infrequently. Bevacizumab

is approved for relapsed disease, as are carmustine wafers and Gliasite brachytherapy.

For newly diagnosed anaplastic gliomas, RT is typically administered as part of the initial therapy. Some advocate chemotherapy first, especially in 1p19q codeleted anaplastic oligodendroglial tumors.<sup>12,13</sup> Based on randomized trials, RT before and after PCV chemotherapy is clearly superior to RT alone for patients with 1p19q codeleted anaplastic oligodendroglial tumors.<sup>98,99</sup>

### Controversies

Treatment for elderly patients (variably defined as older than 60, 65, or 70 years of age, depending on the study) remains controversial. Patients with a good performance status and few comorbidities are often treated according to the same algorithm used for younger patients. However, abbreviated radiotherapy courses appear to be noninferior<sup>107</sup> and are often employed. Temozolomide alone using standard rather than intensified dosing is a reasonable treatment strategy for elderly patients with MGMT-methylated tumors based on comparisons to RT alone, specifically in patients for whom combined-modality therapy is a significant challenge.<sup>112,114</sup> Definitive studies of combined RT and temozolomide restricted only to “elderly” patients have not been completed, and whether chemoradiation using a rapid course of RT is superior to RT or temozolomide alone is under investigation, but it must be borne in mind that the U.S. trials included patients even in their 80s when using combined-modality approaches.

Bevacizumab does not prolong survival when added to RT and temozolomide for newly diagnosed GBM.<sup>90,91</sup> Emerging data suggest that combining bevacizumab with nitrosourea therapy may be superior to bevacizumab or nitrosourea alone for recurrent GBM<sup>136</sup> and this is being further tested in Phase III study by the EORTC.

Treatment of anaplastic gliomas is an area of extreme controversy, with astrocytomas often treated as GBMs and a more variable approach used for oligodendrogliomas. Ongoing trials will attempt to define a standard algorithm based on the 1p/19q deletion status.

### Challenges

Local control of high-grade gliomas remains a vexing problem. In addition, the increased recognition of pseudo-progression as an entity and the possibility of pseudo-response to antiangiogenic therapy such as bevacizumab<sup>167</sup> complicate matters further. A revised set of consensus criteria were recently developed in part to address some of these issues.<sup>129,166</sup> Certainly, correlative clinical follow-up to provide the proper perspective on the health status of the patient will never be abandoned, because imaging will always represent an imperfect surrogate for survival. Although new developments in diagnostic imaging continue to hold out promise for resolution of the diagnostic dilemmas faced by the neurooncology team, to date even the most sophisticated imaging studies (e.g., FDG PET, MRS) have not provided a consistently reliable solution to these and other vexing problems.

### Future Possibilities

Prior dose-escalation trials for GBM, all conducted in the pretemozolomide era, have been uniformly negative beyond 60 Gy. However, it is conceivable that the notion of dose escalation now needs to be revisited in the backdrop of control of microscopic disease by temozolomide enhancing the effect of focal dose-escalation, as well as the potential radioprotection offered by bevacizumab.<sup>53</sup>



The 5-year OS from the EORTC-NCIC study of patients with GBM treated with RT and temozolomide was approximately 10%, and for patients with favorable prognostic factors it approached 30%.<sup>39</sup> Moreover, a patient who lived more than 20 years following the diagnosis of GBM was described, perhaps the longest documented survivor.<sup>168</sup> He had been treated with surgery and partial brain irradiation with no concurrent or maintenance chemotherapy (59 Gy of 6-MV photons in conventional fractionation delivered via a shrinking-field technique). The authors speculated that the outcome may have stemmed from the fact that he had a favorable molecular profile (e.g., methylated *MGMT* promoter, *PTEN* wild-type, and *p53* positive, which the authors termed “triple positive,” similar to the nomenclature of breast cancer). Whether this explained the long survival time is unclear. More importantly, these observations prove that one may strive to create and sustain hope for patients diagnosed with high-grade glioma.

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# TTFields Therapy: Preclinical and Clinical Data

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## INTRODUCTION AND OUTLINE

Tumor Treating Fields (TTFields) is a novel antimitotic cancer treatment modality that works with specialized low-intensity (1–3 V/cm) and intermediate frequency (~200 kHz) electric fields. TTFields for glioblastoma multiforme (GBM) patients are delivered noninvasively through two orthogonal pairs of transducer arrays placed on the shaved scalp. Tumor cells are disrupted during mitosis, with the specific frequency tuned for distinct cancer cell lines, while quiescent cells are not affected.

This chapter covers a short introduction to the basics of electric fields including a description of the mechanisms of action of TTFields. Preclinical findings are outlined and the clinical application of TTFields discussed. The induced electric field distribution within the cranium is explained and illustrated with computational modeling. The last part of the chapter will comment on neuroimaging in patients treated with TTFields including a discussion of response criteria, pseudoprogression, and other treatment-related changes in patients.

## BASIC PRINCIPLES OF TTFIELDS AND PRECLINICAL FINDINGS

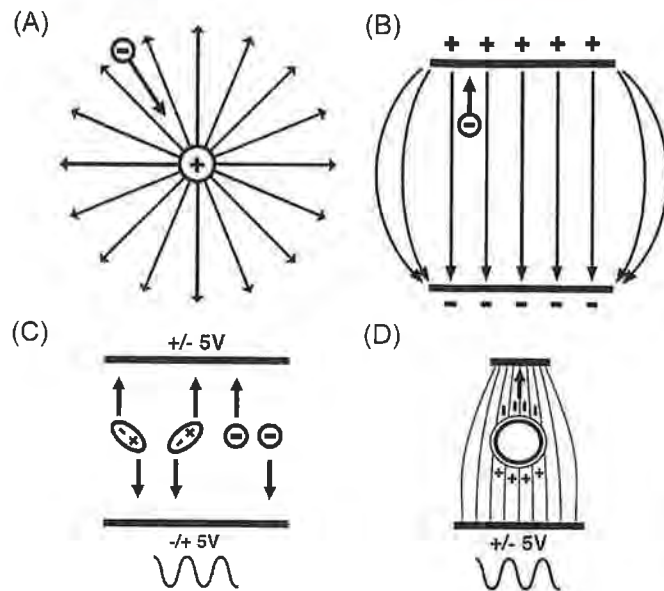
### Introduction to the Physics of Electric Fields

It is important to have an understanding of the physical effects of the electric fields exerted on intracellular macromolecules and proteins. These effects arise from the fact that most of these molecules have a net electric

charge (charged molecules) and/or an electric dipole moment (polar molecules). These physical properties subserve important cellular and biological functions mediated by electrical interactions between such molecules. The charged or polar molecules are also responsive to an applied electric field.

An electric field can be defined as the electric force per unit positive charge. Thus the direction of the electric field is radially outward from a positive charge (Figure 1(A)). In this field, a positive charge will move radially outwards, whereas a negative charge will move radially inwards. Molecules with net charges of opposite signs attract each other whereas molecules with net charges of the same sign repel each other. The electric field can be visualized by drawing directed curved lines (electric field lines) to indicate both the magnitude and the direction of the field. A uniform field is represented by parallel field lines (Figure 1(B)) whereas a nonuniform field is characterized by converging or diverging field lines (Figure 1(A) and (D)).<sup>1</sup> In an electrostatic field, where the source charges remain the same over time, a test charge will move toward the oppositely charged source (Figure 1(B)). In a field with time-varying or alternating source charges this charge will migrate back and forth (Figure 1(C), right). In polar molecules, the spatial separation of the positively and negatively charged poles gives rise to an electric dipole. In a uniform field, no net force is exerted on a dipole; specifically the forces acting at the ends with opposite polarity balance out and there is no movement in either direction.<sup>2</sup> Nonetheless the electric field induces a torque that rotates the dipole so it aligns with the direction of the field





**FIGURE 1** Electric field theory. (A) Opposite charges attract. (B) A constant, uniform, electric field. (C) Charges and dipoles in a time-varying, uniform electric field. (D) A dipole in a time-varying, non-uniform electric field (dielectrophoresis). From Gutin PH and Wong ET (2012) with permission.

(Figure 1(C), left). In a nonuniform field, the forces exerted on the positive and negative poles that make up the dipole are unequal, resulting in a net force and translational motion toward higher field intensity regions (Figure 1(D)). This phenomenon is termed dielectrophoresis, a function of frequency that is thoroughly described by Pohl.<sup>2,3</sup> Dielectrophoretic forces are actionable on neutral particles that are polarizable, proportional to the size of the particle, the degree of nonuniformity of the field, and the difference between dielectric properties of the particle and the suspending medium.

### Mechanisms of Action of TTFields

The effects of the application of electric fields on biological cells are an often-discussed topic within the last few decades. Analytical descriptions and theoretical investigations have led to numerous techniques for cellular characterization and manipulation, which were translated into clinical applications. Low-frequency alternating fields are employed for nerve and muscle stimulation, while high-frequency fields find medical relevance in techniques such as tissue heating or tumor ablation. The biological effects of intermediate frequency fields in the kHz region have not been extensively studied, but investigations have uncovered a number of subtle biological effects on dividing cells.

Many of the subcellular particles that are responsible for mitosis and cytokinesis are highly polar structures. Thus, particles like tubulin, actin, and DNA are very susceptible to an applied electric field. TTFields are

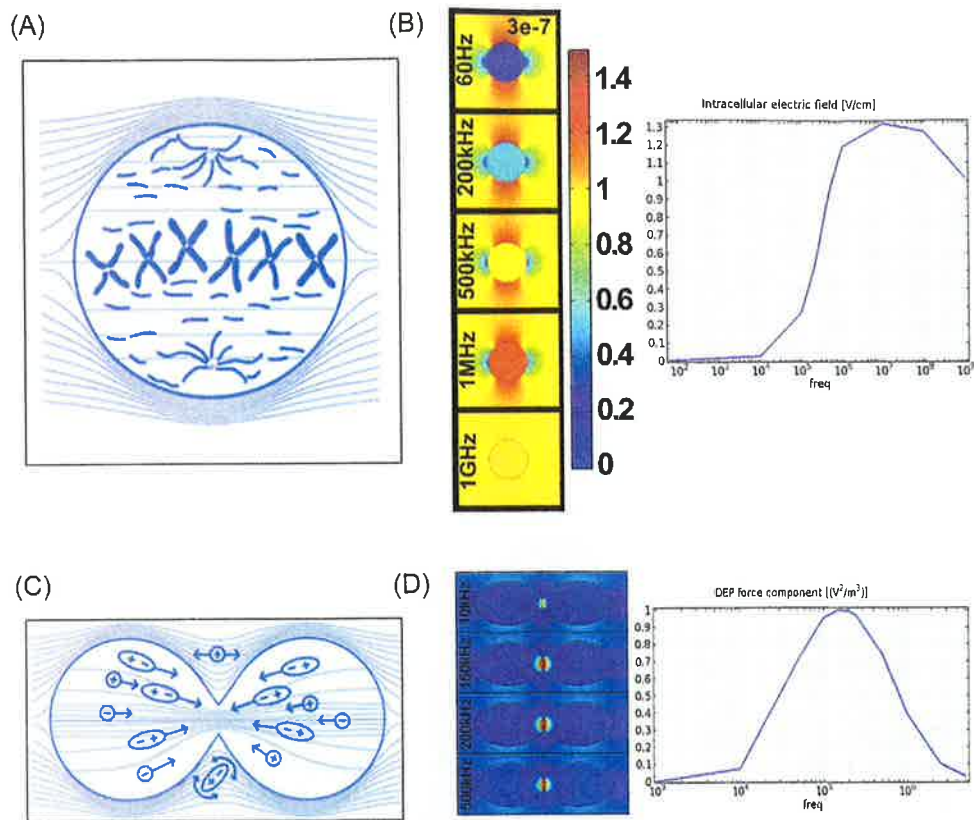
alternating electric fields of intermediate frequency (100–300 kHz) and low intensity (1–3 V/cm). The application of these fields is hypothesized to have distinct effects. For example, TTFields is believed to act by disrupting the formation of a properly functioning mitotic spindle during metaphase and by further disrupting normal cytokinesis during telophase, which leads to apoptosis. The first mechanism of action is explained by the fact that tubulin subunits align in the direction of the applied electric field, which prevents or prolongs the normal polymerization of the mitotic spindle (Figure 2(A)). The penetration of TTFields into the cell's interior was tested with computational modeling. The induced electric field distribution in and around a spherical cell exposed to TTFields during metaphase was computed using Comsol Multiphysics. The kHz frequency range marks a transition region where the intracellular field changes rapidly. For low frequencies, <10 kHz, the intracellular field is almost zero, whereas for high frequencies the impedance of the cell membrane is low and thus the cell becomes “electrically invisible” (Figure 2(B)).

The second mechanism of action results from the specific shape of the cell during anaphase and telophase. Within a dividing cell, the induced electric field is highly nonuniform with increased field intensity at the narrow furrow region. This nonuniform electric field within the cell generates dielectrophoretic forces that act on polar and charged elements in the cell, pushing them toward the cytokinetic furrow and leading to violent blebbing of the plasma membrane (Figure 2(C)).<sup>1</sup> The induced non-uniform field within the cell during different stages of cytokinesis, including the high field intensity region at the furrow, was examined by computational modeling (Figure 2(D), left). The dielectrophoretic force that is proportional to the gradient of the electric field squared was also calculated with this model. The normalized dielectrophoretic force induced in the cell during a late stage of cytokinesis was displayed as a function of frequency (Figure 2(D), right). The shape of the function predicts a very well-defined peak frequency at 150 kHz.

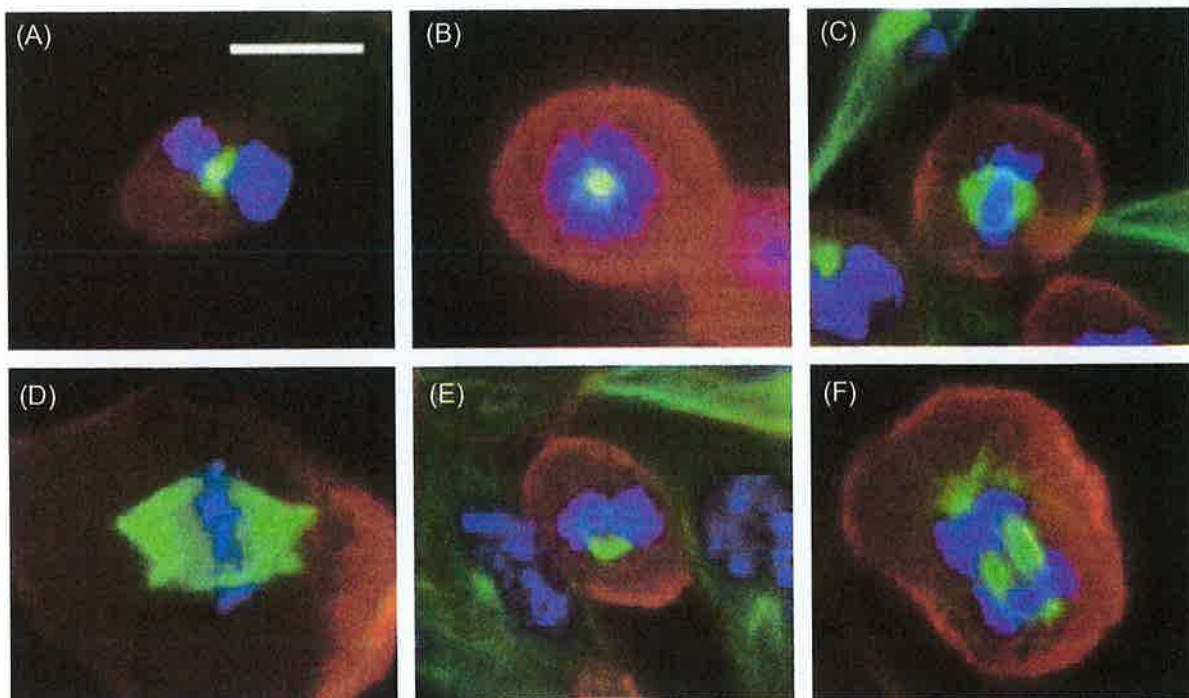
### Cell Biology Effects of TTFields, Preclinical Findings, and Pilot Trials

In order to test these believed mechanisms of actions, *in vitro* experiments were conducted with different cancer cell lines exposed to TTFields. First, field-induced disruptions included violent blebbing, aberrant mitotic exit, and cellular derangement consisting of incompletely or poorly divided cells that have tetraploidy, asymmetric chromosome segregation leading to aneuploidy, or slip-page into a G<sub>0</sub> state (Figure 3).<sup>4,5</sup> Second, once these cells re-enter into the next cycle of mitosis, they may trigger subsequent G<sub>1</sub> or G<sub>2</sub>/M checkpoint leading to apoptosis. Apoptotic cells were readily seen in cell cultures treated





**FIGURE 2** (A) Schematic drawing of the metaphase cell interior during TTFields treatment. Polar particles line up with the impressed field disrupting the proper formation of a functioning mitotic spindle. (B) Corresponding simulation results for the electric field distribution in and around a spherical cell exposed to TTFields of 1 V/cm. The intracellular field intensity is function of frequency. A rapid transition occurs in the kHz range, from a zero field at low frequencies to complete penetration at very high frequencies. (C) Schematic drawing of the telophase cell during TTFields treatment. The hourglass shape of the dividing cell induces a nonuniform field with high field intensities at the furrow region which induces dielectrophoretic force that pulls polarized particles toward it. (D) Corresponding simulation results for the electric field distribution in and around a dividing cell exposed to TTFields of 1 V/cm. The induced intracellular field is highly nonuniform with increased field strength at the furrow region. On the right, the normalized dielectrophoretic force induced in the cell when cytokinesis is almost complete is displayed as a function of frequency. The shape of the function predicts a very well defined peak frequency at 150 kHz. *From Novocure Inc. with permission.*



**FIGURE 3** Immunohistochemical staining of abnormal mitotic figures in TTFields-treated cultures. Malignant melanoma cultures ( $n=4$ ) were treated for 24 h at 100 kHz and then stained with monoclonal antibodies for microtubules (green), actin (red), and DNA (blue). The photomicrographs show exemplary abnormal mitoses including: polyplod prophase (A); rosette (B); ill-separated metaphase (C); multispindled metaphase (D); single-spindled metaphase (E); and asymmetric anaphase (F). *From Kirson ED, Gurovich Z, Schneiderman R, et al (2004) with permission.*



with TTFields. Lastly, the violent membrane blebbing created cytoplasmic stress resulting in the expression of calreticulin on the plasma membrane and secretion of high-mobility group protein B1 into the extracellular space which, in concert, marks the cells for immune destruction.<sup>6</sup> This type of immunogenic cell death that occurs after induction of cellular stress has also been observed after treatment with specific immunostimulating chemotherapies, like oxaliplatin and cyclophosphamide.<sup>7</sup> This is also similar to the abscopal effect from radiation, which relies on the release of intracellular tumor antigen for sensitization of the host's immune system for destruction.<sup>8</sup>

In vitro experiments and experiments in animal tumor models have shown that the efficacy of TTFields depends on the intensity, frequency, and direction of the applied electric fields.<sup>4,9</sup> The cell biology effects of alternating electric fields were tested in various tumor cell lines, including the F98 glioma cell line from the rat. The inhibitory effects of TTFields on proliferation increase with intensity. For rat glioma complete proliferation arrest was observed after a 24h exposure of a TTField intensity of 2.25 V/cm.<sup>4</sup> The optimal frequency varies among cell lines; glioma cells in tissue culture showed the strongest inhibition of cell division at a frequency of 200 kHz.<sup>9</sup> In mouse melanoma cultures, cellular damage was greatest when the applied electric field and the axis of cell division were parallel, in which case there were five times more damaged cells than live cells. This ratio was much closer to one when the angle between the electric field and the axis of cell division was close to 45° and to 90°.<sup>4</sup> Cells that were not actively dividing remained morphologically and functionally intact.<sup>4</sup> The antitumor effects of TTFields were confirmed in an intradermal mouse model for melanoma and an intracranial rat model for glioma.<sup>9</sup> In rats inoculated intracranially with glioma cells, treatment for 6 days using external electrodes to produce an electric field amplitude of 2 V/cm at 200 kHz caused a tumor volume reduction of 42.6% and 53.4% for two and three field directions, respectively, when compared with untreated tumors.<sup>9</sup>

Later, a small pilot trial of TTFields in 10 patients with recurrent glioblastoma demonstrated a median time to tumor progression of 26.1 (range 3.0–124.0) weeks, an overall survival (OS) of 62.2 (range 20.3–124.0) weeks, and a 1-year survival rate of 67.5%.<sup>9</sup> This promising outcome led to a pivotal trial which in turn resulted in the United States Food and Drug Administration (FDA) approval of TTFields as a therapy for recurrent GBM patients, as will be discussed in the next section.

The combined efficacy of TTFields and chemotherapies has been investigated. Using the IC<sub>50</sub> as a measure, there was a 1000-fold drop in the IC<sub>50</sub> of MDA-MB-231 cells when exposed to TTFields and paclitaxel in

combination, as compared to paclitaxel alone.<sup>10</sup> Similar albeit smaller drops in the IC<sub>50</sub>, 20-fold and 150-fold, were observed in the same cell line when exposed to TTFields and doxorubicin as well as TTFields and cyclophosphamide, respectively.

## CLINICAL APPLICATION OF TTFields

### Efficacy of Alternating Electric Fields Therapy for Glioblastoma

The NovoTTF-100A device was approved by the FDA in April 2011 for treating recurrent glioblastoma. The alternating electric fields are delivered by two pairs of transducer arrays positioned orthogonally onto the shaved scalp (Figure 4).<sup>11</sup> The arrays are connected to an electric field generator and a battery pack.<sup>11</sup> The recommended usage is ≥75% compliance or ≥18h daily.

In the pivotal phase III EF-11 clinical trial, the NovoTTF-100A device was demonstrated to have equivalent efficacy when compared to Best Physician's Choice chemotherapy while sparing patients the toxicities associated with systemic chemotherapies.<sup>11,12</sup> As shown in Figure 5, the respective median OS was 6.6 months for NovoTTF-100A (n=120) and 6.0 months for chemotherapy (n=117), with a hazard ratio (HR) of 0.86 (95% confidence interval (CI) 0.66–1.12; P=0.27). The respective median progression-free survival (PFS) was 2.2



**FIGURE 4** The NovoTTF-100A device. Two opposing pairs of transducer arrays are applied to the scalp and the cables are linked to the electric fields generator and a battery pack. From Novocure Inc. with permission.



and 2.1 months, with an HR of 0.81 (95% CI 0.60–1.09;  $P=0.16$ ). The PFS rate at 6 months was 21.4% (95% CI 13.5–29.3) and 15.1% (95% CI 7.8–22.3) ( $P=0.13$ ). The 1-year survival rate was 20% in the NovoTTF-100A cohort and 20% in the chemotherapy cohort. The most common toxicity associated with the NovoTTF-100A device was dermatological irritation, which occurred in 14% of patients with grade I or II severity; none of them had severe grade III or IV toxicity. Notably, the NovoTTF-100A cohort had fewer grade two or greater hematological toxicities compared with the chemotherapy cohort, 3% versus 17%, respectively, and fewer adverse gastrointestinal events, 4% versus 17%. Quality of life analysis (Figure 6) showed that patients treated with NovoTTF-100A had better cognitive and emotional function than those treated with chemotherapy. In contrast, appetite loss, constipation, diarrhea, fatigue, nausea, vomiting, and pain occurred more often in patients treated with chemotherapy than with NovoTTF-100A. Taken together, NovoTTF-100A had equivalent efficacy when compared to chemotherapy in patients with recurrent glioblastoma, while the toxicities associated with the device were mild and compared favorably to chemotherapy.

A post hoc analysis of responders and nonresponders in the EF-11 trial found that secondary glioblastomas were found in a higher frequency in responders than nonresponders in the NovoTTF-100A arm.<sup>13</sup> Additionally, all responders in the NovoTTF-100A arm had a significantly lower dexamethasone burden that statistically varied from the population as a whole, while dexamethasone had a lesser effect in the chemotherapy cohort (Figure 7).<sup>13</sup> Because dexamethasone can induce

global immunosuppression, this finding further suggests that dexamethasone not only predisposes glioblastoma patients to infections, but also likely disables their anticancer immunity.<sup>14</sup>

Mrugala et al.<sup>15</sup> published data from the Patient Registry Dataset (PRiDe) for the 457 recurrent glioblastoma patients treated with NovoTTF-100A across 91 US medical centers. Compared with the EF-11 trial, more patients in the PRiDe received NovoTTF Therapy for first recurrence (33% vs 9%) but had also received previous bevacizumab regimens (55% vs 19%). First or second recurrence (vs third or later recurrence) and no prior bevacizumab use were positive prognostic factors. They found longer median OS with NovoTTF therapy in clinical practice (9.6 months) than in the EF-11 trial (6.6 months), and greater than double the 1-year OS rate (44% vs 20%). These results suggest that NovoTTF can offer favorable clinical benefit to patients with recurrent glioblastoma, while maintaining patient tolerability and safety.

The efficacy of NovoTTF therapy for newly diagnosed glioblastoma is currently being prospectively investigated in EF-14, a randomized multicenter trial of NovoTTF therapy plus adjuvant temozolomide compared with adjuvant temozolomide alone that are administered after completion of initial involved-field cranial irradiation and concomitant daily temozolomide.<sup>16</sup> The primary endpoint is PFS and secondary endpoints include OS, PFS at 6 months, survival at 1 and 2 years, as well as quality of life assessment. All 700 subjects have been accrued and randomized in a 2:1 fashion to NovoTTF therapy plus adjuvant temozolomide:adjuvant temozolomide. The sample size has the power to

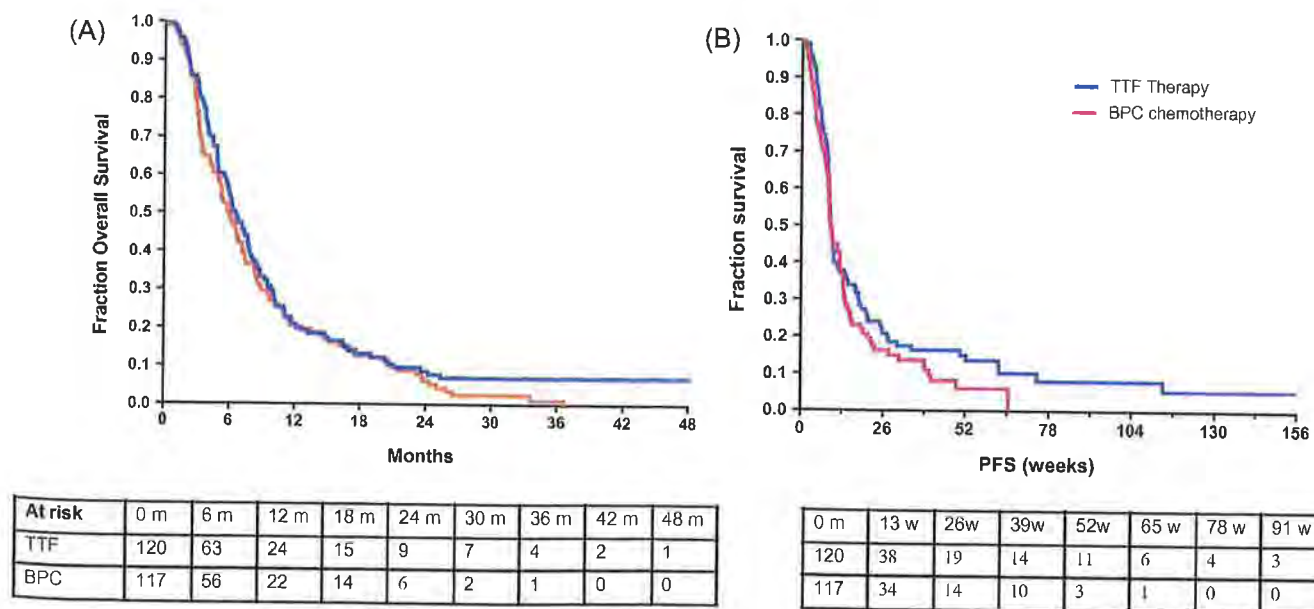
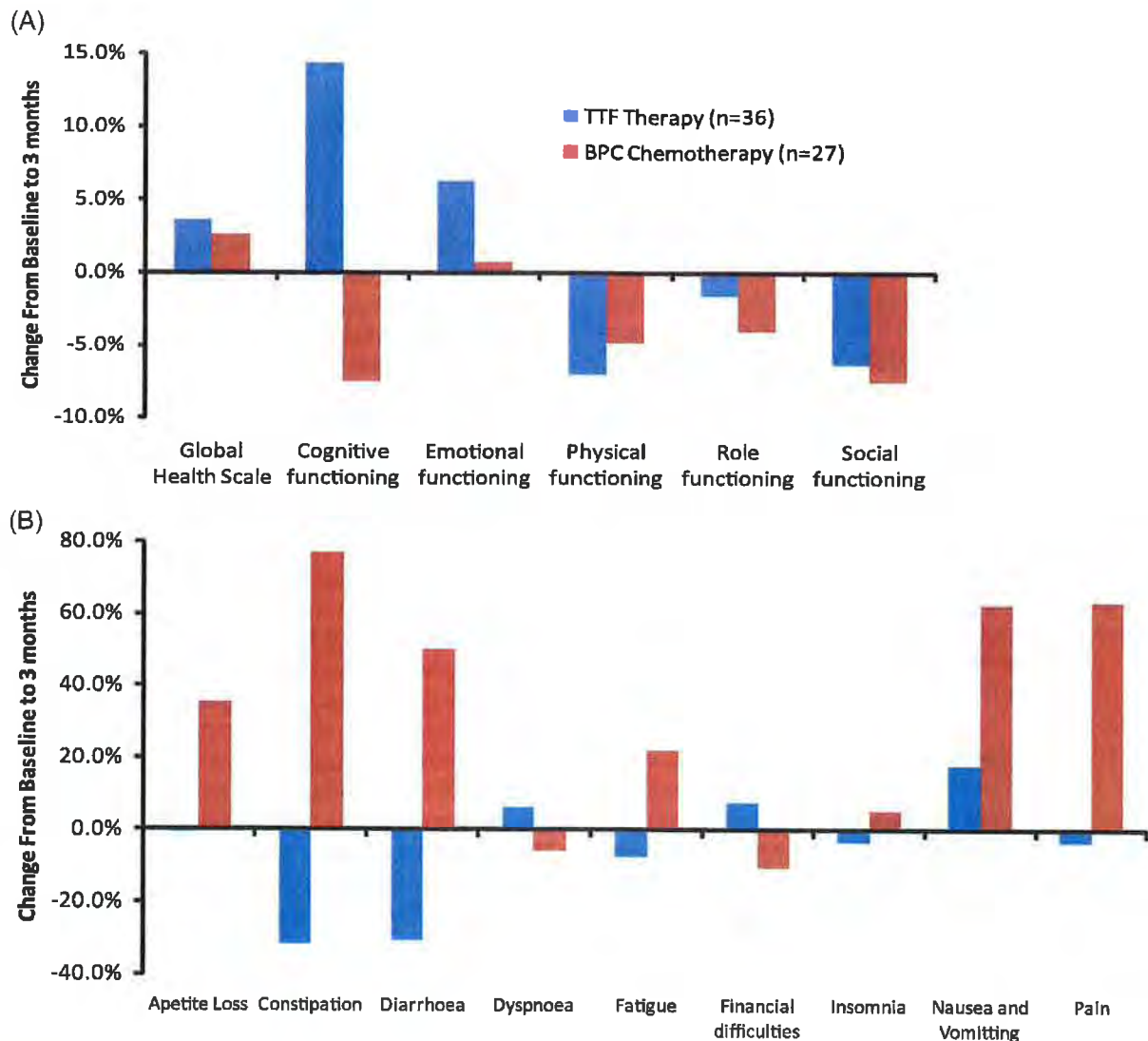


FIGURE 5 Overall survival (A) and progression-free survival (B) Kaplan–Meier curves. From Stupp R, Wong ET, Kanner AA, et al (2012) with permission.



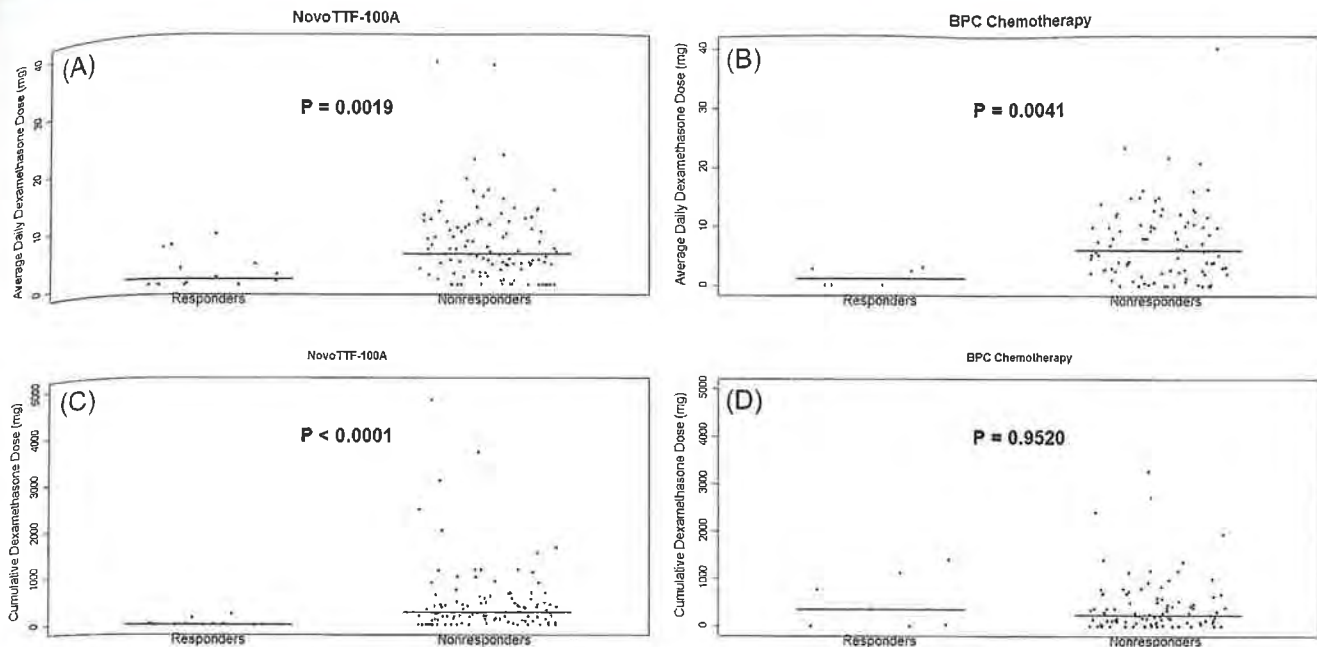


**FIGURE 6** European Organization for Research and Treatment of Cancer quality of life questionnaire (QLQ) C30 longitudinal change from baseline to 3 months. (A) General functional scales (an increase in percentage corresponds to an increase in quality of life). (B) Symptom scales (an increase in percentage corresponds to a decrease in quality of life).

detect an HR of  $<0.78$  for PFS and  $<0.76$  for OS. The data were presented after a prespecified interim analysis of the first 315 subjects after a minimum follow up of 18 months.<sup>17</sup> In the intent-to-treat (ITT) population, there were 210 subjects randomized to the NovoTTF therapy plus adjuvant temozolomide arm and received a median of six cycles of treatment, while 105 subjects were randomized to the adjuvant temozolomide alone arm and received a median of four cycles of treatment. The per protocol (PP) population consisted of subjects that started their second cycle of treatment, or 196 in the former and 84 in the latter. Patient characteristics were balanced with respect to age, Karnofsky performance score, extent of resection, promoter methylation status of O<sup>6</sup>-methylguanine-DNA methyltransferase, and time from diagnosis to randomization. The primary endpoint analysis showed that treatment with NovoTTF therapy

plus adjuvant temozolomide was superior to adjuvant temozolomide alone, with a respective median PFS of 7.1 (95% CI 5.9–8.2) months versus 4.0 (95% CI 3.0–4.3) months (HR=0.6, log rank P=0.0014). The median OS in the former cohort, compared with the latter cohort, was also superior in both the ITT population, 19.6 (95% CI 16.5–24.1) months versus 16.6 (95% CI 13.5–19.1) months, respectively (HR=0.75, log rank P=0.034), and in the PP population, 20.5 (95% CI 16.5–24.1) months versus 15.5 (95% CI 13.5–19.1) months, respectively (HR=0.67, log rank P=0.0072). There were no unexpected adverse events. Expected grade III and IV hematological side effects (12% vs 9%), gastrointestinal disorders (5% vs 2%), and convulsions (7% vs 7%) were similar between the two cohorts. Scalp reaction was more common in the NovoTTF therapy-treated than the temozolomide-only group, 49% vs 5%, respectively, for





**FIGURE 7** Scatter plot of mean daily dexamethasone and cumulative dexamethasone dose in responders and nonresponders. (A) In the NovoTTF-100A cohort, the respective median and mean daily dexamethasone dose was 1.0 and 2.3 (95% CI 0.8–3.8) mg for responders versus 5.2 and 6.8 (95% CI 5.6–8.1) mg for nonresponders ( $P=0.0019$ ). (B) In the BPC cohort, the respective median and mean daily dexamethasone dose was 1.2 and 1.4 (95% CI 0.3–2.4) mg for responders versus 6.0 and 7.2 (95% CI 6.0–8.4) mg for nonresponders ( $P=0.0041$ ). (C) In the NovoTTF-100A cohort, the respective median and mean cumulative dexamethasone dose was 7.1 and 35.9 (95% CI N/A–72.5) mg for responders versus 261.7 and 485.6 (95% CI 347.9–623.4) mg for nonresponders ( $P<0.0001$ ). (D) In the BPC cohort, the respective median and mean cumulative dexamethasone dose was 348.5 and 525.6 (95% CI 96.5–954.7) mg for responders versus 242.3 and 431.0 (95% CI 328.1–533.8) mg for nonresponders ( $P=0.9520$ ). BPC, Best Physician's Choice; CI, confidence interval; N/A, not available.

grade I and II toxicities as well as 7% vs 5%, respectively for grade III and IV toxicities.

## ELECTRIC FIELD DISTRIBUTION WITHIN CRANIUM AND BRAIN

### Experimental Evidence

The dependence of the efficacy of TTFields on the electric field strength has been described earlier. Measurement of the applied electric field in cell cultures and in animals is straightforward. Verification of the field strength inside the human head during TTFields treatment would be desirable, but is fraught with difficulties. A single intracranial measurement has been reported in the literature, showing that an electric field intensity of 1–2 V/cm could be produced in the center of the brain by applying a potential difference of approximately 50 V between the transducer arrays.<sup>9</sup>

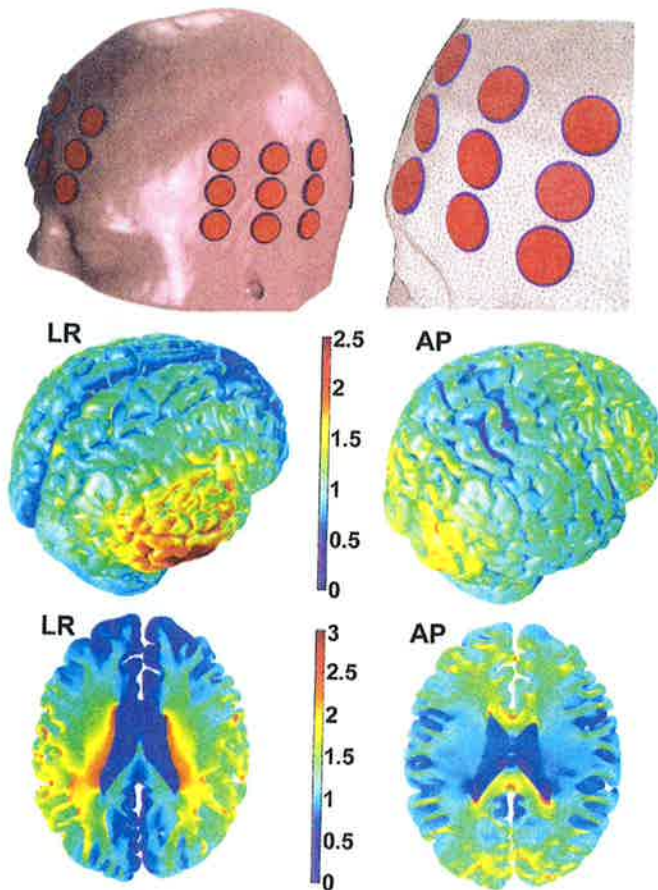
### Computational Model

Computational modeling provides a practical means to estimate the intensity of the electric field in the brain and, more generally, to examine the effect of

the shape and physical properties of the different tissues of the head on the electric field distribution. This can be achieved by combining a realistic three-dimensional representation of the head with a numerical method to calculate the electric field. The three-dimensional model is defined in terms of surfaces that correspond to the boundaries between adjacent tissues. These surfaces are represented by small triangles that make up the surface meshes (see top row of Figure 8). The bulk of the tissue is represented by small volume elements with four triangular surfaces (tetrahedra) that make up the volume meshes. The volume meshes and the surface meshes match at the boundaries. The finite element method is used to solve Maxwell's equations, based on the spatial discretization provided by the volume mesh. The numerical solution of these equations yields an estimate of the electric potential and the electric field within the head (for more details see Miranda et al.<sup>18</sup>).

The head model shown in the top row of Figure 8 was created by segmenting T1- and T2-weighted MR images of a single healthy subject.<sup>18</sup> It consists of five different tissue types: scalp, skull, cerebrospinal fluid (CSF), gray matter (GM), and white matter (WM). The ventricles were assumed to have the same properties as the CSF. Two concentric spheres were introduced





**FIGURE 8** Top row: The scalp surface with transducer arrays in red and gel layers in blue. On the right, a close-up of the anterior array also shows the triangular surface mesh elements. Middle row: The magnitude of the electric field on the cortical surface. Bottom row: The magnitude of the electric field in an axial slice at the level of the ventricles. The electric field is expressed in V/cm.

in the model to mimic the presence of a tumor with a necrotic core placed in the WM near a lateral ventricle. The necrotic core has a diameter of 1.4 cm and is surrounded by a 3 mm active shell. Four transducer arrays that faithfully reproduce those used with the NovoTTF-100A device were placed on the scalp. Each array consists of nine interconnected transducers, capacitively coupled to the scalp. The frequency of the impressed current was set to 200 kHz, and the amplitude of the current through each transducer in an active array was set to 100 mA. Transducer arrays were activated in pairs: the left-right (LR) pair and the anterior-posterior (AP) pair. In addition to the influence of the complex shape of the tissue interfaces, the intensity of the electric field also depends on the electrical properties of the tissues. The values for the electrical conductivity and permittivity used in this model were obtained from the literature (see Table 1). The electric fields were calculated using the finite element method, as described previously.<sup>19</sup> The amplitude of the potential difference

**TABLE 1** Electrical Properties of Tissues and Other Materials Used in this Study<sup>19</sup>

	Conductivity (S/m)	Relative Permittivity
Scalp	0.25	10,000
Skull	0.013	200
CSF	1.79	110
GM	0.25	3000
WM	0.12	2000
Tumor shell	0.24	2000
Tumor core	1.0	110
Gel	0.1	100
Transducer	0	10,000

applied between transducer arrays was 106 V for the AP pair and 75 V for the LR pair.

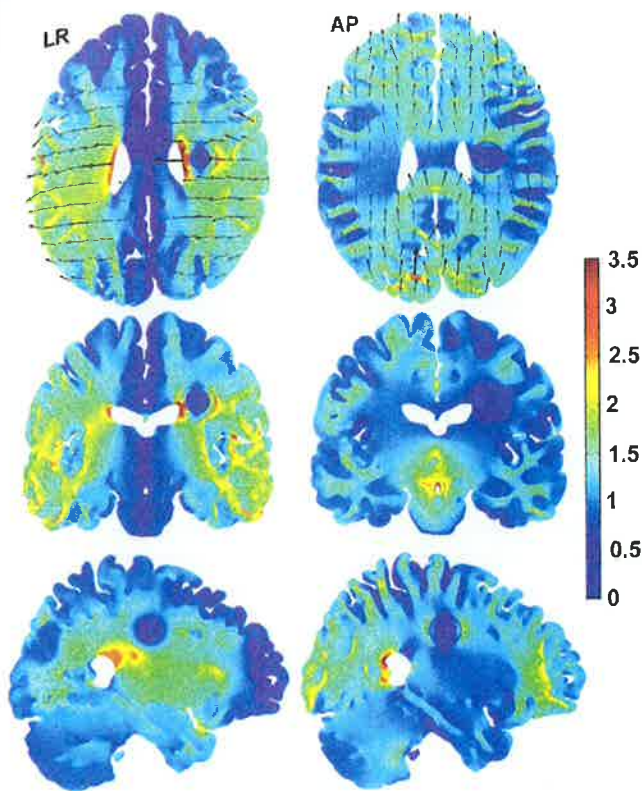
### Modeling Results

The plots in the bottom rows of Figure 8 show the magnitude of the electric field on the cortical surface and in the brain. The distribution is noticeably nonuniform, with local high electric field regions (hotspots) arising far away from the transducers. Nonetheless, in general, the electric field is highest in the regions close to the active arrays and decreases slowly as a function of distance from these arrays. The electric field exceeds 1 V/cm over large areas of the slices shown and also over a large part of the brain in the inferior-superior direction, due to the large dimensions of the arrays (about 6.2 cm by 8.4 cm). In both configurations, the magnitude of the electric field exceeded 1 V/cm in more than 60% of the total brain volume (WM+GM), and it exceeded 2 V/cm in less than 5% of the total brain volume.

The observed nonuniform field distribution is due to tissue heterogeneity. At a boundary, the component of the electric field that is perpendicular to that boundary is enhanced in the low conductivity tissue and reduced in the high conductivity tissue, giving rise to a discontinuity in the electric field intensity. This effect is particularly visible near the ventricles in the LR configuration, where part of the WM-CSF boundary is perpendicular to the applied electric field (see bottom row in Figure 8). It is also visible near WM-GM interfaces under the transducers, but the effect is less marked because the difference between the conductivities of these two tissues is not as great as at the WM-CSF interface (see AP and LR fields). Note that the electric field in the ventricles is extremely low due to the high conductivity of CSF.

The electric field in and around the tumor is also affected by tissue heterogeneity.<sup>20</sup> In this model, the presence of a high conductivity necrotic core boosts





**FIGURE 9** The magnitude of the electric field in axial (top row), coronal (middle row), and sagittal (bottom row) slices through the virtual lesion. The arrows in the axial slice indicate the direction of the alternating field. The electric field is expressed in V/cm.

the electric field in the surrounding tumor and WM (Figure 9). Again, the hotspots occur where the interfaces are perpendicular to the applied electric field. This implies that in the high electric field regions in the tumor, the field direction is always approximately perpendicular to the tissue boundaries. Also, the existence of these directional effects points to another advantage of applying the electric field in two or more directions: different directions may increase the field in different parts of the tumor. The plots in this figure also show that the electric field intensity at the tumor site is strongly influenced by the proximity to the ventricles. It is also influenced by the distance between the tumor and the active arrays, which suggests that a simple rule to place the arrays on the scalp is to minimize their distance to the tumor.

### Future Modeling Developments

The computational model used to calculate the electric field inside the head is based on classical physics and well-known numerical methods, and therefore the results are thought to be reliable. Nevertheless, there is an uncertainty in the predicted values that is due mainly

to the uncertainty in the dielectric properties of the tissues. Given the range of values reported in the literature, the uncertainty in the electric field could amount to about 50%. In the future, we plan to reduce this uncertainty in new head models by incorporating electrical conductivity data derived from diffusion tensor imaging (DTI). This is particularly important for calculating the electric fields within the tumor since the data available in the literature are scarce and so DTI data may provide better estimates of the conductivity in the necrotic core, the cancerous shell, and the edema that surrounds it. DTI does not provide information about the permittivity of the tissues, but this property has a small impact on the electric field in the frequency range of TTFields. Also, DTI data may be useful for image segmentation as it may provide a better distinction of the tumor borders and a better definition of the edema region.

### IMAGING IN PATIENTS TREATED WITH TTFields THERAPY

TTFields represents a unique treatment for glioblastoma that does not fall into the traditional categories of surgery, radiation, or chemotherapy. Compared with conventional cytotoxic therapies intended to kill tumor cells, TTFields represent a novel anticancer treatment that inhibits cell division by interfering with the formation of the mitotic spindle and by affecting polar molecules from metaphase to telophase.<sup>4,9</sup> Interpretation of imaging changes caused by treatment with TTFields therefore relies on understanding the mechanism of action and familiarity with potentially variable patterns of treatment response as well as failure. This section will discuss standard response criteria, typical imaging changes seen with conventional and investigational therapies, and early experience with TTFields.

### Response Criteria

Most clinical treatment decisions rely on changes in the size of the enhancing tumor(s): increasing size and/or number represents tumor progression and requires a change in treatment, while decreasing size and/or number represent tumor response. In 1990, in order to facilitate comparisons of treatments being tested in different clinical trials Macdonald et al.<sup>21</sup> proposed standardized response criteria that defined progressive disease (PD) as  $\geq 25\%$  increase in the size of enhancing tumor(s) (measured bidimensionally by taking the sum of the product of perpendicular diameters) or the presence of new enhancing tumor(s). Recognizing that newer treatments could induce transient increases in enhancing lesion(s) representing treatment related changes rather than tumor, the Macdonald criteria were updated in 2010 by



the Response Assessment in Neuro-Oncology (RANO) working group with several important additions.<sup>22</sup> First, an allowance was made for early treatment-related changes termed pseudoprogression. Any increase in size of enhancing lesion(s)  $\leq 3$  months after completion of radiation therapy located within the high-dose radiation field (80% isodose line) were no longer considered to represent PD, unless there was histopathologic evidence of tumor. New enhancing lesion(s) located outside the high-dose radiation field were still considered PD. After the first 3 months, RANO also defined recurrence as  $\geq 25\%$  increase of the enhancing lesions. Second, in recognition of progression of nonenhancing tumor in the setting of antiangiogenic therapy (e.g., bevacizumab), "significant" increases in T2/fluid attenuated inversion recovery (FLAIR) hyperintense signal became a new criterion for PD. This pseudoresponse, where rapid decrease in enhancing disease is not correlated with tumor response, is a well-described phenomenon with antiangiogenic therapies but unlikely to occur with treatments that do not directly affect the blood-brain barrier.

### Pseudoprogression and Other Treatment-Related Changes

Pseudoprogression is a subacute treatment induced phenomenon that presents with new and/or increasing enhancing lesion(s) that spontaneously stabilize or resolve without further therapy. Thought to represent an inflammatory response to treatment,<sup>23,24</sup> pseudoprogression is most familiar in high-grade gliomas after treatment with radiation therapy and concomitant daily temozolomide as per Stupp et al.<sup>25</sup> Similar treatment-related changes with transient imaging worsening have been described with other older therapies,<sup>26-28</sup> as well as newer therapies—notably immune modulating agents.<sup>29</sup> Wolchok et al.<sup>29</sup> described treatment response and improved survival in patients with systemic metastatic melanoma treated with ipilimumab, despite an increased burden of enhancing lesions and the presence of new enhancing lesions. They therefore proposed new immune-related response criteria to better characterize these treatment-related changes and avoid overestimations of PD, and may also be applicable after treatment with TTFields, despite the more common use of RANO criteria.

Diagnosis of treatment-related changes often requires clinical and imaging follow-up to determine stability or resolution on subsequent scans, or repeat surgery with histopathologic confirmation of necrosis without tumor. Accurate determination of treatment-related changes versus tumor is necessary, because the two involve antithetical management. Treatment-related changes may require steroids or other therapy for relief of symptomatic edema and/or mass effect, or in unrelenting cases of

radiation necrosis may also necessitate surgery or antiangiogenic therapy.<sup>30-32</sup> Patients should in many cases continue their current, probably effective therapy. In contrast, recurrent tumor requires discontinuation of current ineffective therapy and consideration of new therapy.

### Advanced Imaging Techniques

The changes in size used by most response criteria to determine treatment response may occasionally lag behind alterations in tumor biology, where effective therapy may decrease metabolically active tumor that remains stable in size. In other situations, changes in size may be misleading when accelerated cell killing, treatment-related inflammatory changes, and blood-brain barrier disruption—as occurs with pseudoprogression—may induce an increase in enhancing lesions and edema to mimic worsening tumor. To complement traditional magnetic resonance imaging (MRI) sequences, advanced imaging techniques enable measurement of biological changes that do not depend upon changes in size. These technologies interrogate different aspects of tumor pathophysiology and may provide independent predictors of patient outcome, confirmation of suspected progression or treatment effects in clinical trials, as well as measurement of biological effects of investigational drugs. Popular techniques that are briefly discussed below include MR perfusion, MR spectroscopy, and positron emission tomography (PET).

Dynamic contrast enhanced (DCE) T1, dynamic susceptibility contrast T2\*, and arterial spin labeling perfusion MR techniques provide information about tumor microvasculature, neoangiogenesis, and blood-brain barrier disruption. Multiple studies have shown utility in differentiating between recurrent tumor and radiation injury, including pseudoprogression. For example, while both recurrent tumor and radiation injury can show increases in size of enhancing and T2/FLAIR lesions, an increase in the relative cerebral blood volume, as measured by MR perfusion, is seen with recurrent tumors but not in radiation necrosis.<sup>24,33-35</sup> Increases in perfusion in the setting of tumor progression are related to increased microscopic vessel density from tumor neoangiogenesis. The enhancing lesions of radiation injury instead reflect increased leakiness with inflammatory mediators and blood-brain barrier disruption.

MR spectroscopy provides the semiquantification of metabolites that can characterize the composition of a lesion in the brain. This can aid in the diagnosis of radiation injury, which typically demonstrates low choline (a cell membrane marker) and possibly high lipid/lactate peaks (indicating necrosis). In contrast, tumors typically demonstrate high choline and low *N*-acetylaspartate (NAA), which may also be expressed as a choline/NAA ratio.<sup>36,37</sup>



PET uses metabolic tracers (most commonly, the glucose analogue 2-deoxy-2-( $^{18}\text{F}$ )fluoro-D-glucose (FDG)) to study brain lesion metabolism. FDG is preferentially taken up by hypermetabolic tumor cells, and not by radiation injury. Although studies have suggested accuracy for distinguishing tumor recurrence from radiation changes, the high basal uptake of FDG in the brain that results in high background signal continues to represent a technical challenge.<sup>38-40</sup> Other nonFDG PET agents may prove to be more sensitive and specific to treatment changes, but these are still being investigated in clinical trials and not widely available.

### Imaging in Patients Treated with NovoTTF Therapy: Early Experience

The unique mechanisms of action of TTFields and its effects on tumor biology present additional challenges to traditional response criteria based on changes in the size of the enhancing tumor. The electric fields interfere with the organized coalescence of the mitotic spindle and affects polar molecules from metaphase to telophase to prevent cell division at the  $G_1$  or  $G_2/M$  checkpoints. As cells are required to be in active mitosis, any immune-mediated apoptosis induced by treatment may therefore be expected to require some time to occur.

Some patients may have a delay in radiographic response after treatment with TTFields. In a post hoc analysis of pilot and phase III trial data, Vymazal and Wong<sup>41</sup> reported that the median time to response was delayed by 5.2 months. This delay suggests that the relatively slow TTFields induced tumor cell death may be insufficient in symptomatic patients with rapidly progressive tumors. This is despite the fact that tumor cells with active mitoses are most susceptible to the electrical fields. While delayed, the response may be durable with a median response duration of 12.9 months.<sup>41</sup>

Some patients may also demonstrate transient increases in enhancing lesion size that do not represent tumor growth (Figure 10). This is similar to the pseudoprogression that is most familiar after standard radiation therapy and temozolomide chemotherapy. In these delayed responders with initial tumor growth, the median time to reversal of tumor growth was 4 months (95% CI, 2.3–7.4).<sup>41</sup> Villano et al.<sup>42</sup> described a patient who survived greater than 6 years using TTFields as monotherapy, where initial growth of the enhancing recurrent glioblastoma was followed by slow decrease. These observations are consistent with kinetic model stimulations in which tumor growth is maximum at 1 month followed by a reduction of tumor volume to 35% near 6.8 months, which is equivalent to a 50% decrease or partial response in bidimensional tumor measurement according to Macdonald or RANO criteria.<sup>41</sup>

Given the possibility for delayed treatment response, caution should be applied when interpreting worsening imaging results in patients treated with TTFields. New enhancing lesions within the treatment field should be considered possible tumor progression or treatment-related change (e.g., pseudoprogression), and investigated using additional or advanced imaging to confirm the diagnosis. Confirmation should be sought using advanced imaging, with the choice of MR perfusion, spectroscopy, PET/computed tomography (CT) or other techniques depending on the local expertise and available technology. New enhancing lesions outside the treatment field, however, should be considered tumor progression as per the RANO criteria.

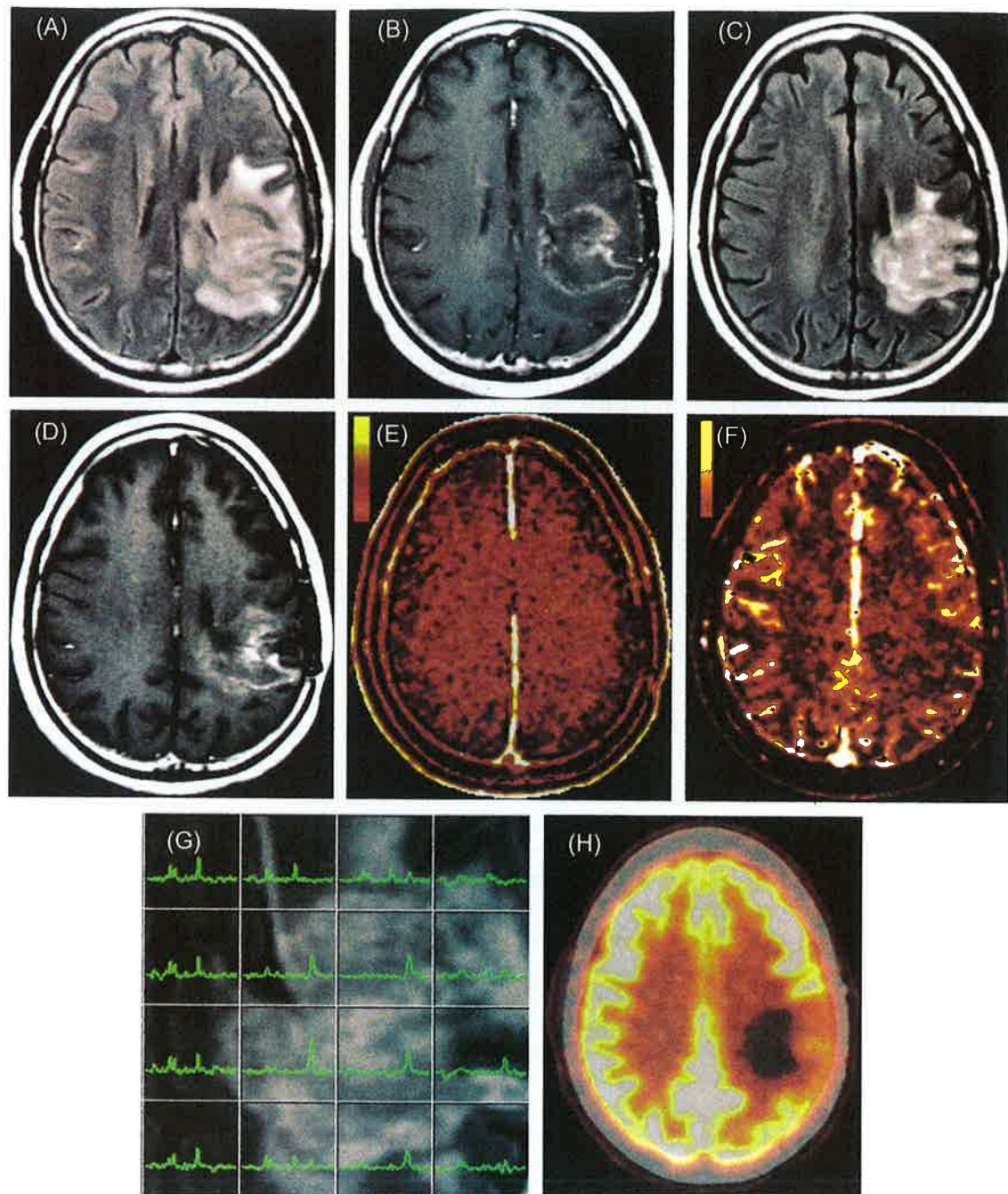
Another consideration in evaluating response in patients treated with TTFields pertains to the treatment fields themselves. Treatment fields are nonuniform and different parts of the brain may receive different “doses” based on field strength and positioning.<sup>19</sup> Tumor progression may occur more frequently at the edges of the treatment fields due to lowered field strengths at the periphery.<sup>20</sup> It is important to recognize that treatment design, field strength, and cell size may all play a role in out-of-field recurrences. If recurrence occurs, new enhancing tumors outside of the tumor treatment field may be treated by adjusting the treatment field maps using the NovoTAL software.

## CONCLUSIONS

Alternating electric fields represent a novel treatment strategy for patients with recurrent glioblastoma, and a viable alternative to conventional chemotherapies. This is because these fields interfere with tumor cell division at a different part of the cell cycle, rendering it unique to other oncolytic agents. In vitro, TTFields can be combined with specific chemotherapies to achieve at least an additive anticancer effect. The modeling study clearly demonstrates the need for patient-specific head models in order to predict the electric field as accurately as possible. Such models could be used in a retrospective study to establish the link between the electric field distribution and treatment outcome, both positive and negative. They could also be used prospectively for treatment planning. In this case, the positions of the transducer arrays and the current delivered through each pair could be used a priori to optimize the electric fields delivered to the tumor could be determined a priori. Typical optimization criteria would include high intensity and uniformity of the electric field in the area containing tumor and edema, as well as low field intensity in the surrounding brain tissues.<sup>43,44</sup>

Early clinical experience has demonstrated that the NovoTTF therapy-induced cell death may in some





**FIGURE 10** Patient with glioblastoma 18 months after completion of radiation therapy and temozolomide followed by adjuvant temozolomide, with bevacizumab added 5 months earlier for recurrent tumor. Axial FLAIR (A) and contrast T1-weighted (B) images demonstrate nonenhancing hyperintense and enhancing disease, respectively, indicating failure of treatment. The bevacizumab was discontinued and the patient began CPT-11 and NovoTTF-100A. Two months later, there is decreased nonenhancing (C) and enhancing (D) disease. DCE MRI perfusion shows no leakiness on the Ktrans map (E) or hyperperfusion on the plasma volume map (F) multivoxel MRI spectroscopy (G) demonstrates a lipid/lactate peak with decreased remaining metabolites, and FDG PET/CT (H) confirms absence of hypermetabolic activity. These are all consistent with absence of active high-grade tumor. CPT-11 was discontinued 17 months later due to fatigue and excessive number of cycles, while NovoTTF-100A was continued as monotherapy for another 5 months before another progression (not shown). BCNU (bis-chloroethylnitrosourea) was added to the treatment regimen for the patient who survived another 2 years.

patients result in a delayed treatment response or transient worsening before response. Since it may be unclear whether this worsening detected by conventional MRI is due to tumor progression or evolving

treatment-related changes, advanced imaging techniques, and follow up should be performed to confirm the diagnosis whenever possible. Future experience will help determine the rate and time frame of these



treatment-related changes, and the optimal imaging strategy to diagnose treatment response or tumor progression.

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## Introduction

There have been numerous exciting advances in cancer care, and specifically to the field of neuro-oncology. Basic science research has dramatically increased the understanding of tumor biology, and better defined the role of cancer stem cells in maintaining tumor growth and resistance to therapy. The result of this work has been the identification of numerous potential targets for therapy, making neuro-oncology a prime area for translational research. Clinically, a coordinated team approach among surgical, medical, neuroimaging, and radiation oncology and pathology ensures a timely and accurate diagnosis, and that the most up-to-date and effective treatment options are available to the patient for their specific cancer. This chapter reviews some of the promising areas in diagnostic testing, neuroimaging, and therapies that are impacting the understanding of brain tumors and brain tumor care.

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## Background/Epidemiology

### Metastasis

The most common malignant intracranial tumors are metastases, which spread hematogenously from systemic solid tumors or hematologic malignancies (Fig. 22.1a, b). Less frequently, systemic cancer may spread to the central nervous system (CNS) as dural (Fig. 22.2) or leptomeningeal metastasis (Fig. 22.3a, b). CNS metastases are often a manifestation of advanced and progressive systemic cancer, but rarely may be the presenting feature of an occult malignancy. The likelihood of developing brain metastasis varies greatly depending on the primary cancer site. Individuals with lung cancer develop brain metastasis at an estimated incidence of 19.9 %, breast cancer 5.1 %, and GU malignancies 1 % or less [1].

Brain metastases characteristically present with focal neurologic dysfunction related to the site of involvement, or progressively worsening headache. Typical radiographic features are a peripherally enhancing lesion or lesions occurring at the cortical/subcortical junction. Posterior fossa lesions, cystic lesions, and tumors with an imaging appearance similar to primary brain tumors may also occur. Headache, confusion/depressed level of consciousness, and cranial neuropathies are the most common presenting signs and symptoms of meningeal carcinomatosis, with